THERAPEUTIC AGENTS USEFUL FOR TREATING PAIN

This application claims the benefit of U.S. Provisional application no. 60/412,847, filed September 24, 2002, the entire disclosure of which is incorporated by reference herein in its entirety.

1. FIELD OF THE INVENTION

The present invention relates to Hydroxyiminopiperazine Compounds, compositions comprising an effective amount of a Hydroxyiminopiperazine Compound and methods for treating or preventing a Condition, such as pain, comprising administering to an animal in need thereof an effective amount of a Hydroxyiminopiperazine Compound.

2. BACKGROUND OF THE INVENTION

Pain is the most common symptom for which patients seek medical advice and treatment. Pain can be acute or chronic. While acute pain is usually self-limited, chronic pain persists for 3 months or longer and can lead to significant changes in a patient's personality, lifestyle, functional ability and overall quality of life (K.M. Foley, *Pain, in Cecil Textbook of Medicine* 100-107 (J.C. Bennett and F. Plum eds., 20th ed. 1996)).

Pain has been traditionally managed by administering non-opioid analgesics, such as acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflusinal, and naproxen; or opioid analgesics, including morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, and oxymorphone. *Id.*

Urinary incontinence (UI) is uncontrollable urination, generally caused by bladder-detrusor-muscle instability. UI affects people of all ages and levels of physical health, both in health care settings and in the community at large. At present, UI afflicts 15-30% of elderly people living at home, one-third of those living in acute-care settings, and at least one-half of those living in long-term care institutions (R.M. Resnick, *Lancet* 346:94 (1995)). Persons having UI are predisposed to also having urinary-tract infections, pressure ulcers, perineal rashes and urosepsis. Psychosocially, UI is associated with embarrassment, social stigmatization, depression and a risk of institutionalization (Herzo *et al.*, *Annu. Rev. Gerontol. Geriatr.* 9:74 (1989)). Economically, the costs of UI are great; in the United States alone, health-care costs associated with UI are over $15 billion per annum.

Physiologic bladder contraction results in large part from acetylcholine-induced stimulation of post-ganglionic muscarinic-receptor sites on bladder smooth muscle.

Treatments for UI include the administration of drugs having bladder-relaxant properties, which help to control bladder-detrusor-muscle overactivity. For example, anticholinergics such as propantheline bromide and glycopyrrolate, and combinations of smooth-muscle relaxants such as a combination of racemic oxybutynin and dicyclomine or an anticholinergic, have been used to treat UI (*See, e.g.*, A.J. Wein, *Urol. Clin. N. Am.* 22:557-577 (1995); Levin *et al.*, *J. Urol.* 128:396-398 (1982); Cooke *et al.*, *S. Afr. Med. J.* 63:3 (1983); R.K. Mirakhur *et al.*, *Anaesthesia* 38:1195-1204 (1983)). These drugs are not effective, however, in all patients having uninhibited bladder contractions. Administration of anticholinergic medications represent the mainstay of this type of treatment.

None of the existing commercial drug treatments for UI, however, has achieved complete success in all classes of UI patients, nor has treatment occurred without significant adverse side effects. For example, drowsiness, dry mouth, constipation, blurred vision, headaches, tachycardia, and cardiac arrhythmia, which are related to the anticholinergic activity of traditional anti-UI drugs, can occur frequently and adversely affect patient compliance. Yet despite the prevalence of unwanted anticholinergic effects in many patients, anticholinergic drugs are currently prescribed for patients having UI. *The Merck Manual of Medical Information* 631-634 (R. Berkow ed., 1997).

About 1 in 10 people develop an ulcer. Ulcers develop as a result of an imbalance between acid-secretory factors, also known as "aggressive factors," such as stomach acid, pepsin, and *Helicobacter pylori* infection, and local mucosal-protective factors, such as secretion of bicarbonate, mucus, and prostaglandins.

Treatment of ulcers typically involves reducing or inhibiting the aggressive factors. For example, antacids such as aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, and calcium bicarbonate can be used to neutralize stomach acids. Antacids, however, can cause alkalosis, leading to nausea, headache, and weakness. Antacids can also interfere with the absorption of other drugs into the blood stream and cause diarrhea.

H_2 antagonists, such as cimetidine, ranitidine, famotidine, and nizatidine, are also used to treat ulcers. H_2 antagonists promote ulcer healing by reducing gastric acid and digestive-enzyme secretion elicited by histamine and other H_2 agonists in the stomach and duodenum. H_2 antagonists, however, can cause breast enlargement and impotence in men, mental changes (especially in the elderly), headache, dizziness, nausea, myalgia, diarrhea, rash, and fever.

H^+, K^+ - ATPase inhibitors such as omeprazole and lansoprazole are also used to treat ulcers. H^+, K^+ - ATPase inhibitors inhibit the production of enzymes used by

the stomach to secrete acid. Side effects associated with H^+, K^+ - ATPase inhibitors include nausea, diarrhea, abdominal colic, headache, dizziness, somnolence, skin rashes, and transient elevations of plasma activities of aminotransferases.

Sucraflate is also used to treat ulcers. Sucraflate adheres to epithelial cells and is believed to form a protective coating at the base of an ulcer to promote healing. Sucraflate, however, can cause constipation, dry mouth, and interfere with the absorption of other drugs.

Antibiotics are used when *Helicobacter pylori* is the underlying cause of the ulcer. Often antibiotic therapy is coupled with the administration of bismuth compounds such as bismuth subsalicylate and colloidal bismuth citrate. The bismuth compounds are believed to enhance secretion of mucous and HCO_3^-, inhibit pepsin activity, and act as an antibacterial against *H. pylori*. Ingestion of bismuth compounds, however, can lead to elevated plasma concentrations of Bi^{+3} and can interfere with the absorption of other drugs.

Prostaglandin analogues, such as misoprostal, inhibit secretion of acid and stimulate the secretion of mucous and bicarbonate and are also used to treat ulcers, especially ulcers in patients who require nonsteroidal anti-inflammatory drugs. Effective oral doses of prostaglandin analogues, however, can cause diarrhea and abdominal cramping. In addition, some prostaglandin analogues are abortifacients.

Carbenoxolone, a mineral corticoid, can also be used to treat ulcers. Carbenoxolone appears to alter the composition and quantity of mucous, thereby enhancing the mucosal barrier. Carbenoxolone, however, can lead to Na^+ and fluid retention, hypertension, hypokalemia, and impaired glucose tolerance.

Muscarinic cholinergic antagonists such as pirenzapine and telenzapine can also be used to reduce acid secretion and treat ulcers. Side effects of muscarinic cholinergic antagonists include dry mouth, blurred vision, and constipation. *The Merck Manual of Medical Information* 496-500 (R. Berkow ed., 1997) and *Goodman and Gilman's The Pharmacological Basis of Therapeutics* 901-915 (J. Hardman and L. Limbird eds., 9th ed. 1996).

Inflammatory-bowel disease (IBD) is a chronic disorder in which the bowel becomes inflamed, often causing recurring abdominal cramps and diarrhea. The two types of IBD are Crohn's disease and ulcerative colitis.

Crohn's disease, which can include regional enteritis, granulomatous ileitis, and ileocolitis, is a chronic inflammation of the intestinal wall. Crohn's disease occurs equally in both sexes and is more common in Jews of eastern-European ancestry. Most

cases of Crohn's disease begin before age 30 and the majority start between the ages of 14 and 24. The disease typically affects the full thickness of the intestinal wall. Generally the disease affects the lowest portion of the small intestine (ileum) and the large intestine, but can occur in any part of the digestive tract.

Early symptoms of Crohn's disease are chronic diarrhea, crampy abdominal pain, fever, loss of appetite, and weight loss. Complications associated with Crohn's disease include the development of intestinal obstructions, abnormal connecting channels (fistulas), and abscesses. The risk of cancer of the large intestine is increased in people who have Crohn's disease. Often Crohn's disease is associated with other disorders such as gallstones, inadequate absorption of nutrients, amyloidosis, arthritis, episcleritis, aphthous stomatitis, erythema nodosum, pyoderma gangrenosum, ankylosing spondylitis, sacroilitis, uveitis, and primary sclerosing cholangitis. There is no known cure for Crohn's disease.

Cramps and diarrhea, side effects associated with Crohn's disease, can be relieved by anticholinergic drugs, diphenoxylate, loperamide, deodorized opium tincture, or codeine. Generally, the drug is taken orally before a meal.

Broad-spectrum antibiotics are often administered to treat the symptoms of Crohn's disease. The antibiotic metronidazole is often administered when the disease affects the large intestine or causes abscesses and fistulas around the anus. Long-term use of metronidazole, however, can damage nerves, resulting in pins-and-needles sensations in the arms and legs. Sulfasalazine and chemically related drugs can suppress mild inflammation, especially in the large intestine. These drugs, however, are less effective in sudden, severe flare-ups. Corticosteroids, such as prednisone, reduce fever and diarrhea and relieve abdominal pain and tenderness. Long-term corticosteroid therapy, however, invariably results in serious side effects such as high blood-sugar levels, increased risk of infection, osteoporosis, water retention, and fragility of the skin. Drugs such as azathioprine and mercaptourine can compromise the immune system and are often effective for Crohn's disease in patients that do not respond to other drugs. These drugs, however, usually need 3 to 6 months before they produce benefits and can cause serious side effects such as allergy, pancreatitis, and low white-blood-cell count.

When Crohn's disease causes the intestine to be obstructed or when abscesses or fistulas do not heal, surgery can be necessary to remove diseased sections of the intestine. Surgery, however, does not cure the disease, and inflammation tends to recur where the intestine is rejoined. In almost half of the cases a second operation is needed. *The Merck Manual of Medical Information* 528-530 (R. Berkow ed., 1997).

Ulcerative colitis is a chronic disease in which the large intestine becomes inflamed and ulcerated, leading to episodes of bloody diarrhea, abdominal cramps, and fever. Ulcerative colitis usually begins between ages 15 and 30, however, a small group of people have their first attack between ages 50 and 70. Unlike Crohn's disease, ulcerative colitis never affects the small intestine and does not affect the full thickness of the intestine. The disease usually begins in the rectum and the sigmoid colon and eventually spreads partially or completely through out the large intestine. The cause of ulcerative colitis is unknown. Treatment of ulcerative colitis is directed to controlling inflammation, reducing symptoms, and replacing lost fluids and nutrients.

Irritable-bowel syndrome (IBS) is a disorder of motility of the entire gastrointestinal tract, causing abdominal pain, constipation, and/or diarrhea. IBS affects three-times more women than men.

There are two major types of IBS. The first type, spastic-colon type, is commonly triggered by eating, and usually produces periodic constipation and diarrhea with pain. Mucous often appears in the stool. The pain can come in bouts of continuous dull aching pain or cramps, usually in the lower abdomen. The person suffering from spastic-colon type IBS can also experience bloating, gas, nausea, headache, fatigue, depression, anxiety, and difficulty concentrating. The second type of IBS usually produces painless diarrhea or constipation. The diarrhea can begin suddenly and with extreme urgency. Often the diarrhea occurs soon after a meal and can sometimes occur immediately upon awakening.

Treatment of IBS typically involves modification of an IBS-patient's diet. Often it is recommended that an IBS patient avoid beans, cabbage, sorbitol, and fructose. A low-fat, high-fiber diet can also help some IBS patients. Regular physical activity can also help keep the gastrointestinal tract functioning properly. Drugs such as propantheline that slow the function of the gastrointestinal tract are generally not effective for treating IBS. Antidiarrheal drugs, such as diphenoxylate and loperamide, help with diarrhea. *The Merck Manual of Medical Information* 525-526 (R. Berkow ed., 1997).

Certain pharmaceutical agents have been administered for treating addiction. U.S. Patent No. 5,556,838 to Mayer *et al.* discloses the use of nontoxic NMDA-blocking agents co-administered with an addictive substance to prevent the development of tolerance or withdrawal symptoms. U.S. Patent No. 5,574,052 to Rose *et al.* discloses co-administration of an addictive substance with an antagonist to partially block the pharmacological effects of the substance. U.S. Patent No. 5,075,341 to Mendelson *et al.*

discloses the use of a mixed opiate agonist/antagonist to treat cocaine and opiate addiction. U.S. Patent No. 5,232,934 to Downs discloses administration of 3-phenoxypyridine to treat addiction. U.S. Patents No. 5,039,680 and 5,198,459 to Imperato *et al.* disclose using a serotonin antagonist to treat chemical addiction. U.S. Patent No. 5,556,837 to Nestler et. al. discloses infusing BDNF or NT-4 growth factors to inhibit or reverse neurological adaptive changes that correlate with behavioral changes in an addicted individual. U.S. Patent. No. 5,762,925 to Sagan discloses implanting encapsulated adrenal medullary cells into an animal's central nervous system to inhibit the development of opioid intolerance. U.S. Patent No. 6,204,284 to Beer *et al.* discloses racemic (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane for use in the prevention or relief of a withdrawal syndrome resulting from addiction to drugs and for the treatment of chemical dependencies.

Parkinson's disease is a clinical syndrome comprising bradykinesia (slowness and poverty of movement), muscular rigidity, resting tremor (which usually abates during voluntary movement), and an impairment of postural balance leading to disturbance of gait and falling. The features of Parkinson's disease are a loss of pigmented, dopaminergic neurons of the substantia nigra pars compacta and the appearance of intracellular inclusions known as Lewy bodies (*Goodman and Gillman's The Pharmaceutical Basis of Therapeutics* 506 (9th ed. 1996)). Without treatment, Parkinson's disease progresses to a rigid akinetic state in which patients are incapable of caring for themselves. Death frequently results from complications of immobility, including aspiration pneumonia or pulmonary embolism. Drugs commonly used for the treatment of Parkinson's disease include carbidopa/levodopa, pergolide, bromocriptine, selegiline, amantadine, and trihexyphenidyl hydrochloride. There remains, however, a need for drugs useful for the treatment of Parkinson's disease and having an improved therapeutic profile.

Anxiety is a fear, apprehension, or dread of impending danger often accompanied by restlessness, tension, tachycardia, and dyspnea. Currently, benzodiazepines are the most commonly used anti-anxiety agents for generalized anxiety disorder. Benzodiazepines, however, carry the risk of producing impairment of cognition and skilled motor functions, particularly in the elderly, which can result in confusion, delerium, and falls with fractures. Sedatives are also commonly prescribed for treating anxiety. The azapirones, such as buspirone, are also used to treat moderate anxiety. The azapirones, however, are less useful for treating severe anxiety accompanied with panic attacks.

Epilepsy is a disorder characterized by the tendency to have recurring seizures. Examples of drugs for treating a seizure and epilepsy include carbamazepine, ethosuximide, gabapentin, lamotrignine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, bemzodiaepines, gabapentin, lamotrigine, γ-vinyl GABA, acetazolamide, and felbamate. Anti-seizure drugs, however, can have side effects such as drowsiness; hyperactivity; hallucinations; inability to concentrate; central and peripheral nervous system toxicity, such as nystagmus, ataxia, diplopia, and vertigo; gingival hyperplasia; gastrointestinal disturbances such as nausea, vomiting, epigastric pain, and anorexia; endocrine effects such as inhibition of antidiuretic hormone, hyperglycemia, glycosuria, osteomalacia; and hypersensitivity such as scarlatiniform rash, morbilliform rash, Stevens-Johnson syndrome, systemic lupus erythematosus, and hepatic necrosis; and hematological reactions such as red-cell aplasia, agranulocytosis, thrombocytopenia, aplastic anemia, and megaloblastic anemia. *The Merck Manual of Medical Information* 345-350 (R. Berkow ed., 1997).

A stroke or cerebrovascular accident, is the death of brain tissue (cerebral infarction) resulting from the lack of blood flow and insufficient oxygen to the brain. A stroke can be either ischemic or hemorrhagic. Examples of drugs for treating strokes include anticoagulants such as heparin, drugs that break up clots such as streptokinase or tissue plasminogen activator, and drugs that reduce swelling such as mannitol or corticosteroids. *The Merck Manual of Medical Information* 352-355 (R. Berkow ed., 1997).

Pruritus is an unpleasant sensation that prompts scratching. Pruritus can be attributed to dry skin, scabies, dermatitis, herpetiformis, atopic dermatitis, *pruritus vulvae et ani*, miliaria, insect bites, pediculosis, contact dermatitis, drug reactions, urticaria, urticarial eruptions of pregnancy, psoriasis, lichen planus, lichen simplex chronicus, exfoliative dermatitis, folliculitis, bullous pemphigoid, and fiberglass dermatitis. Conventionally, pruritus is treated by phototherapy with ultraviolet B or PUVA or with therapeutic agents such as naltrexone, nalmefene, danazol, tricyclics, and antidepressants.

Selective antagonists of the metabotropic glutamate receptor 5 ("mGluR5") have been shown to exert analgesic activity in *in vivo* animal models (K. Walker *et al.*, *Neuropharmacology* 40:1-9 (2000) and A. Dogrul *et al.*, *Neuroscience Letters*, 292(2):115-118 (2000)).

Selective antagonists of the mGluR5 receptor have also been shown to exert anxiolytic and anti-depressant activity in *in vivo* animal models (E. Tatarczynska *et al.*, *Br.*

J. Pharmacol. 132(7):1423-1430 (2001) and P.J.M. Will *et al.*, *Trends in Pharmacological Sciences* 22(7):331-37 (2001)).

Selective antagonists of the mGluR5 receptor have also been shown to exert anti-Parkinson activity *in vivo* (K. J. Ossowska *et al.*, *Neuropharmacology* 41(4):413-20 (2001) and P.J.M. Will *et al.*, *Trends in Pharmacological Sciences* 22(7):331-37 (2001)).

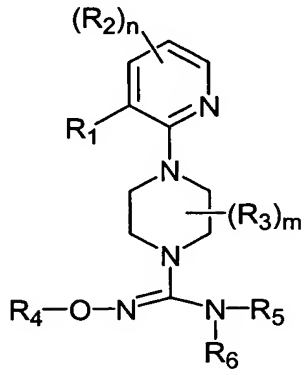
Selective antagonists of the mGluR5 receptor have also been shown to exert anti-dependence activity *in vivo* (C. Chiamulera *et al.*, *Nature Neuroscience* 4(9):873-74 (2001)).

There remains, however, a clear need in the art for new drugs useful for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, amyotrophic lateral sclerosis ("ALS"), dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression.

Citation of any reference in Section 2 of this application is not to be construed as an admission that such reference is prior art to the present application.

3. SUMMARY OF THE INVENTION

The present invention encompasses compounds having the formula (I):



(I)

and pharmaceutically acceptable salts thereof, wherein:

R_1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R_2 is independently:

(a) -halo, -CN, -OH, NO_2, $-O(C_1\text{-}C_6)alkyl$, or $-NH_2$;

(b) $-(C_1\text{-}C_{10})alkyl$, $-(C_2\text{-}C_{10})alkenyl$, $-(C_2\text{-}C_{10})alkynyl$, $-(C_3\text{-}C_{10})cycloalkyl$, $-(C_8\text{-}C_{14})bicycloalkyl$, $-(C_8\text{-}C_{14})tricycloalkyl$, $-(C_5\text{-}C_{10})cycloalkenyl$, $-(C_8\text{-}C_{14})bicycloalkenyl$, $-(C_8\text{-}C_{14})tricycloalkenyl$, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})aryl$, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, NO_2, $-O(C_1\text{-}C_6)alkyl$, or $-NH_2$;

(b) $-(C_1\text{-}C_{10})alkyl$, $-(C_2\text{-}C_{10})alkenyl$, $-(C_2\text{-}C_{10})alkynyl$, $-(C_3\text{-}C_{10})cycloalkyl$, $-(C_8\text{-}C_{14})bicycloalkyl$, $-(C_8\text{-}C_{14})tricycloalkyl$, $-(C_5\text{-}C_{10})cycloalkenyl$, $-(C_8\text{-}C_{14})bicycloalkenyl$, $-(C_8\text{-}C_{14})tricycloalkenyl$, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})aryl$, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

R_4 is -H, $-(C_1\text{-}C_{10})alkyl$, $-C(O)R_9$, or $-C(O)NHR_9$;

R_5 is -H or -(C_1-C_{10})alkyl;

R_6 is:

(a) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(b) -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

each R_7 and R_8 is independently -(C_1–C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_{10})$_2$, -CH=NR_{10}, -NR_{10}OH, -OR_{10}, -C(O)R_{10}, -C(O)OR_{10}, -OC(O)R_{10}, -OC(O)OR_{10}, -SR_{10}, -S(O)R_{10}, or -S(O)$_2$$R_{10}$;

each R_9 is -H, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -OH, -N(R_{10})$_2$, -CH=NR_{10}, -NR_{10}OH, -OR_{10}, or -SR_{10};

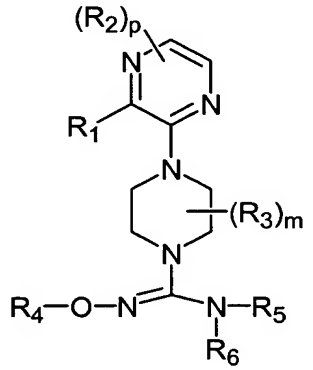
each R_{10} is independently -H, -(C_1-C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

each halo is independently -F, -Cl, -Br, or -I;

n is an integer ranging from 0 to 3; and

m is an integer ranging from 0 to 2.

The present invention encompasses compounds having the formula (II):



(II)

and pharmaceutically acceptable salts thereof, wherein:

R_1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R_2 is independently:

(a) -halo, -CN, -OH, NO_2, $-O(C_1-C_6)alkyl$, or $-NH_2$;

(b) $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_8-C_{14})tricycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_8-C_{14})bicycloalkenyl$, $-(C_8-C_{14})tricycloalkenyl$, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})aryl$, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, NO_2, $-O(C_1-C_6)alkyl$, or $-NH_2$;

(b) $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_8-C_{14})tricycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_8-C_{14})bicycloalkenyl$, $-(C_8-C_{14})tricycloalkenyl$, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})aryl$, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

R_4 is -H, $-(C_1-C_{10})alkyl$, $-C(O)R_9$, or $-C(O)NHR_9$;

R_5 is -H or $-(C_1-C_{10})alkyl$;

R_6 is:

(a) $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_8-C_{14})tricycloalkyl$, $-(C_5-C_{10})cycloalkenyl$,$-(C_8-C_{14})bicycloalkenyl$, $-(C_8-C_{14})tricycloalkenyl$, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(b) -phenyl, -naphthyl, $-(C_{14})aryl$, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

each R_7 and R_8 is independently $-(C_1–C_6)alkyl$, $-(C_2–C_6)alkenyl$, $-(C_2–C_6)alkynyl$, $-(C_3–C_8)cycloalkyl$, $-(C_5-C_8)cycloalkenyl$, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R_{10})_2$, $-CH=NR_{10}$,

$-NR_{10}OH$, $-OR_{10}$, $-COR_{10}$, $-C(O)OR_{10}$, $-OC(O)R_{10}$, $-OC(O)OR_{10}$, $-SR_{10}$, $-S(O)R_{10}$, or $-S(O)_2R_{10}$;

each R_9 is -H, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_8)$cycloalkyl, $-(C_5-C_8)$cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -OH, $-N(R_{10})_2$, $-CH=NR_{10}$, $-NR_{10}OH$, $-OR_{10}$, or $-SR_{10}$;

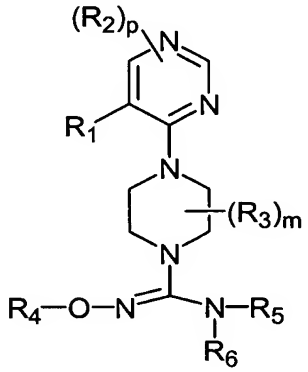
each R_{10} is independently -H, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_8)$cycloalkyl, $-(C_5-C_8)$cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each halo is independently -F, -Cl, -Br, or -I;

p is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (III):



(III)

and pharmaceutically acceptable salts thereof, wherein:

R_1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R_2 is independently:

(a) -halo, -CN, -OH, NO_2,$-O(C_1-C_6)$alkyl, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, NO_2, -O(C_1-C_6)alkyl, or -NH_2;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

R_4 is -H, -(C_1-C_{10})alkyl, -C(O)R_9, or -C(O)NHR_9;

R_5 is -H or -(C_1-C_{10})alkyl;

R_6 is:

(a) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(b) -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

each R_7 and R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_{10})$_2$, -CH=NR_{10}, -NR_{10}OH, -OR_{10}, -COR_{10}, -C(O)OR_{10}, -OC(O)R_{10}, -OC(O)OR_{10}, -SR_{10}, -S(O)R_{10}, or -S(O)$_2$$R_{10}$;

each R_9 is -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -OH, -N(R_{10})$_2$, -CH=NR_{10}, -NR_{10}OH, -OR_{10}, or -SR_{10};

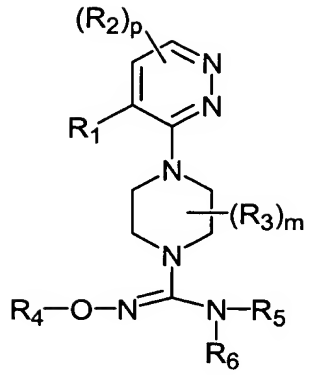
each R_{10} is independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

each halo is independently -F, -Cl, -Br, or -I;

p is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (IV):



(IV)

and pharmaceutically acceptable salts thereof, wherein:

R_1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R_2 is independently:

(a) -halo, -CN, -OH, NO_2, $-O(C_1\text{-}C_6)alkyl$, or $-NH_2$;

(b) $-(C_1\text{-}C_{10})alkyl$, $-(C_2\text{-}C_{10})alkenyl$, $-(C_2\text{-}C_{10})alkynyl$, $-(C_3\text{-}C_{10})cycloalkyl$, $-(C_8\text{-}C_{14})bicycloalkyl$, $-(C_8\text{-}C_{14})tricycloalkyl$, $-(C_5\text{-}C_{10})cycloalkenyl$, $-(C_8\text{-}C_{14})bicycloalkenyl$, $-(C_8\text{-}C_{14})tricycloalkenyl$, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})aryl$, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, NO_2, $-O(C_1\text{-}C_6)alkyl$, or $-NH_2$;

(b) $-(C_1\text{-}C_{10})alkyl$, $-(C_2\text{-}C_{10})alkenyl$, $-(C_2\text{-}C_{10})alkynyl$, $-(C_3\text{-}C_{10})cycloalkyl$, $-(C_8\text{-}C_{14})bicycloalkyl$, $-(C_8\text{-}C_{14})tricycloalkyl$, $-(C_5\text{-}C_{10})cycloalkenyl$, $-(C_8\text{-}C_{14})bicycloalkenyl$, $-(C_8\text{-}C_{14})tricycloalkenyl$, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})aryl$, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

R_4 is -H, $-(C_1\text{-}C_{10})alkyl$, $-C(O)R_9$, or $-C(O)NHR_9$;

R_5 is -H or $-(C_1\text{-}C_{10})alkyl$;

R_6 is:

(a) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(b) -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

each R_7 and R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_{10})$_2$, -CH=NR_{10}, -NR_{10}OH, -OR_{10}, -C(O)OR_{10}, -OC(O)R_{10}, -OC(O)OR_{10}, -SR_{10}, -S(O)R_{10}, or -S(O)$_2$$R_{10}$;

each R_9 is -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -OH, -N(R_{10})$_2$, -CH=NR_{10}, -NR_{10}OH, -OR_{10}, or -SR_{10};

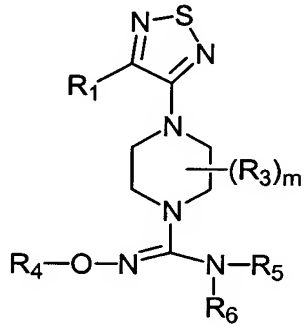
each R_{10} is independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

each halo is independently -F, -Cl, -Br, or -I;

p is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (V):



(V)

and pharmaceutically acceptable salts thereof, wherein:

R_1 is -halo, -CH_3, -NO_2, -CN, -OH, -OCH_3, -NH_2, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

each R_3 is independently:

(a) -halo, -CN, -OH, NO_2, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

R_4 is -H, $-(C_1-C_{10})$alkyl, $-C(O)R_9$, or $-C(O)NHR_9$;

R_5 is -H or $-(C_1-C_{10})$alkyl;

R_6 is:

(a) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(b) -phenyl, -naphthyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

each R_7 and R_8 is independently $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_8)$cycloalkyl, $-(C_5-C_8)$cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R_{10})_2$, $-CH=NR_{10}$, $-NR_{10}OH$, $-OR_{10}$, $-COR_{10}$, $-C(O)OR_{10}$, $-OC(O)R_{10}$, $-OC(O)OR_{10}$, $-SR_{10}$, $-S(O)R_{10}$, or $-S(O)_2R_{10}$;

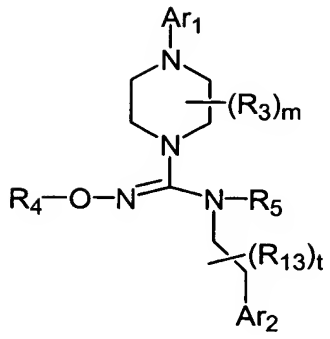
each R_9 is -H, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_8)$cycloalkyl, $-(C_5-C_8)$cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -OH, $-N(R_{10})_2$, $-CH=NR_{10}$, $-NR_{10}OH$, $-OR_{10}$, or $-SR_{10}$;

each R_{10} is independently -H, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_8)$cycloalkyl, $-(C_5-C_8)$cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each halo is independently -F, -Cl, -Br, or -I; and

m is an integer ranging from 0 to 2.

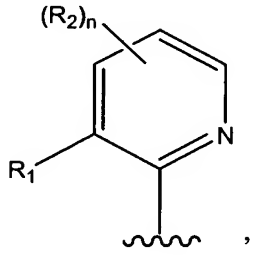
The present invention also encompasses compounds having the formula (VI):



(VI)

and pharmaceutically acceptable salts thereof, wherein:

Ar_1 is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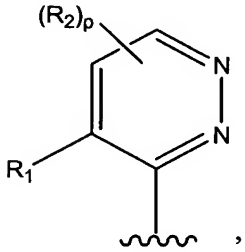
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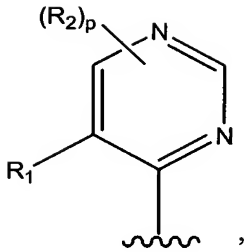
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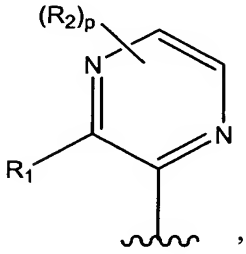
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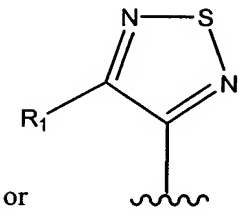
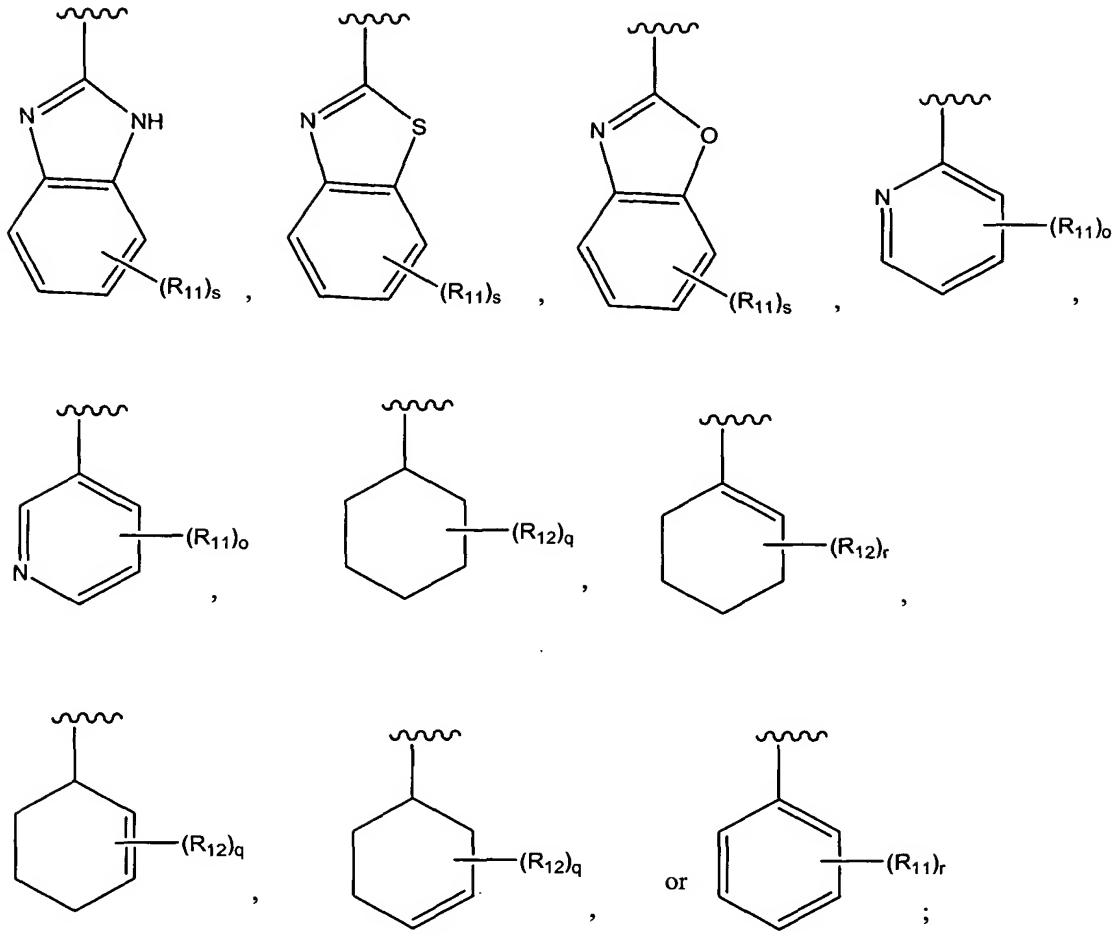

or ;

Ar_2 is



R_1 is -H, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R_2 is independently:

(a) -halo, -CN, -OH, NO_2, $-O(C_1\text{-}C_6)alkyl$, or $-NH_2$;

(b) $-(C_1\text{-}C_{10})alkyl$, $-(C_2\text{-}C_{10})alkenyl$, $-(C_2\text{-}C_{10})alkynyl$, $-(C_3\text{-}C_{10})cycloalkyl$, $-(C_8\text{-}C_{14})bicycloalkyl$, $-(C_8\text{-}C_{14})tricycloalkyl$, $-(C_5\text{-}C_{10})cycloalkenyl$, $-(C_8\text{-}C_{14})bicycloalkenyl$, $-(C_8\text{-}C_{14})tricycloalkenyl$, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})aryl$, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, NO_2, $-O(C_1\text{-}C_6)alkyl$, or $-NH_2$;

(b) $-(C_1\text{-}C_{10})alkyl$, $-(C_2\text{-}C_{10})alkenyl$, $-(C_2\text{-}C_{10})alkynyl$, $-(C_3\text{-}C_{10})cycloalkyl$, $-(C_8\text{-}C_{14})bicycloalkyl$, $-(C_8\text{-}C_{14})tricycloalkyl$, $-(C_5\text{-}C_{10})cycloalkenyl$, $-(C_8\text{-}C_{14})bicycloalkenyl$, $-(C_8\text{-}C_{14})tricycloalkenyl$, -(3- to 7-membered)heterocycle, or -(7- to 10-

membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

R_4 is -H, -(C_1-C_{10})alkyl, -C(O)R_9, or -C(O)NHR_9;

R_5 is -H or -(C_1-C_{10})alkyl;

each R_7 and R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_{10})$_2$, -CH=NR_{10}, -NR_{10}OH, -OR_{10}, -COR$_{10}$, -C(O)OR_{10}, -OC(O)R_{10}, -OC(O)OR_{10}, -SR_{10}, -S(O)R_{10}, or -S(O)$_2$$R_{10}$;

each R_9 is -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -OH, -N(R_{10})$_2$, -CH=NR_{10}, -NR_{10}OH, -OR_{10}, or -SR_{10};

each R_{10} is independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

each R_{11} and R_{12} is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR$_7$, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$;

each R_{13} is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, CH_2(halo), or -halo;

each halo is independently -F, -Cl, -Br, or -I;

s is an integer ranging from 0 to 4;

o is an integer ranging from 0 to 4;

q is an integer ranging from 0 to 6;

r is an integer ranging from 0 to 5;

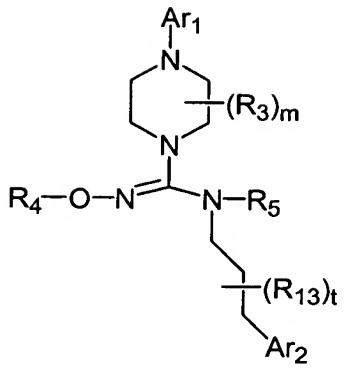
t is an integer ranging from 0 to 2;

p is an integer ranging from 0 to 2;

n is an integer ranging from 0 to 3; and

m is an integer ranging from 0 to 2.

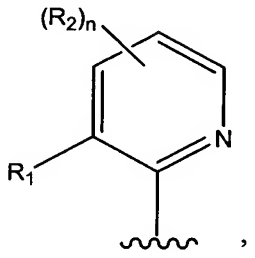
The present invention also encompasses compounds having the formula (VII):



(VII)

and pharmaceutically acceptable salts thereof, wherein:

Ar_1 is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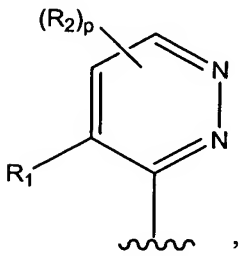
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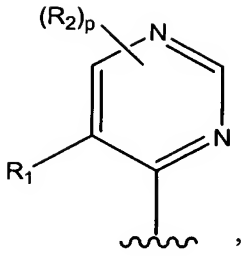
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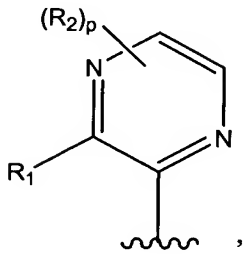
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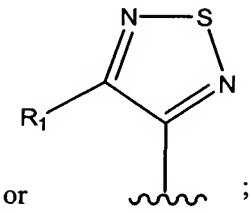
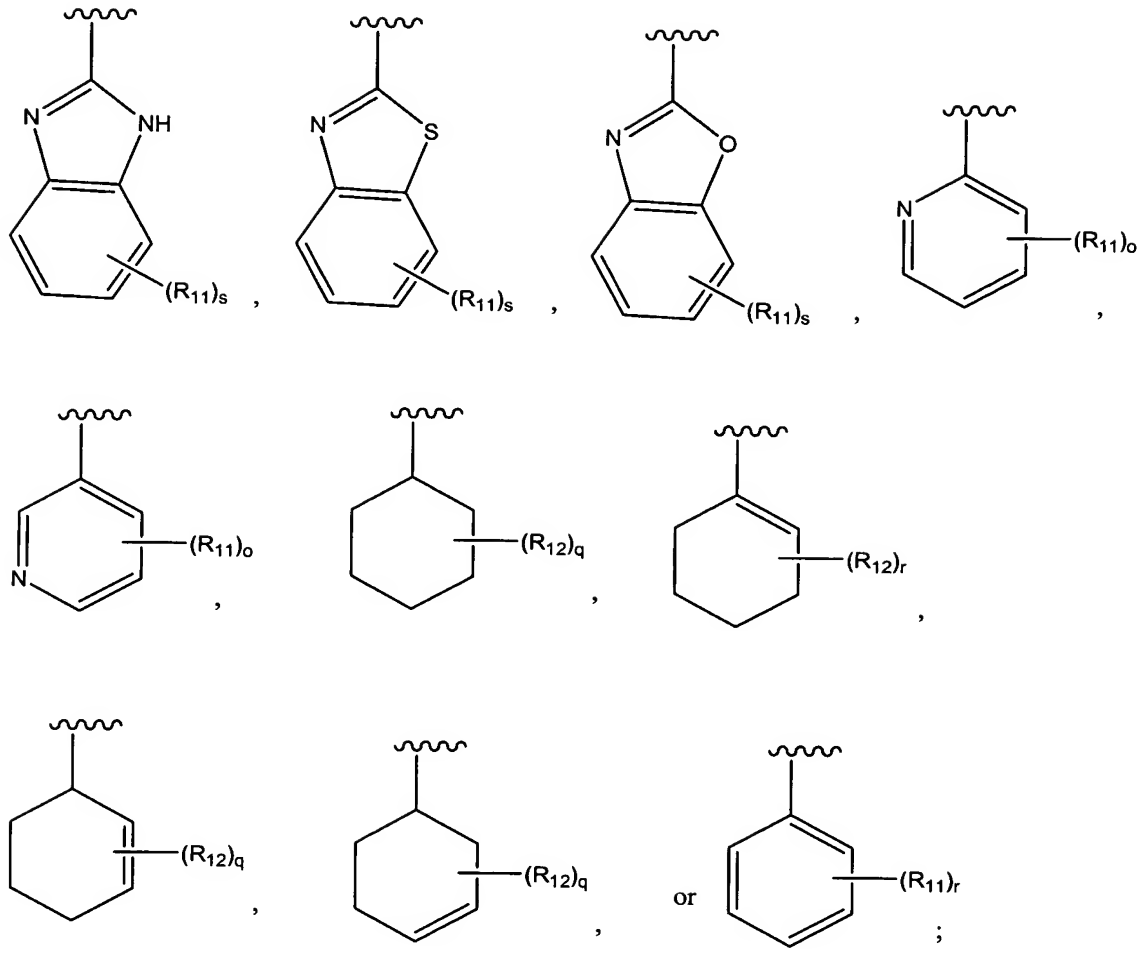

or ;

Ar_2 is



R_1 is -H, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R_2 is independently:

(a) -halo, -CN, -OH, NO_2, $-O(C_1\text{-}C_6)alkyl$, or $-NH_2$;

(b) $-(C_1\text{-}C_{10})alkyl$, $-(C_2\text{-}C_{10})alkenyl$, $-(C_2\text{-}C_{10})alkynyl$, $-(C_3\text{-}C_{10})cycloalkyl$, $-(C_8\text{-}C_{14})bicycloalkyl$, $-(C_8\text{-}C_{14})tricycloalkyl$, $-(C_5\text{-}C_{10})cycloalkenyl$, $-(C_8\text{-}C_{14})bicycloalkenyl$, $-(C_8\text{-}C_{14})tricycloalkenyl$, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})aryl$, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

each R_3 is independently:

(a) -halo, -CN, -OH, NO_2, $-O(C_1\text{-}C_6)alkyl$, or $-NH_2$;

(b) $-(C_1\text{-}C_{10})alkyl$, $-(C_2\text{-}C_{10})alkenyl$, $-(C_2\text{-}C_{10})alkynyl$, $-(C_3\text{-}C_{10})cycloalkyl$, $-(C_8\text{-}C_{14})bicycloalkyl$, $-(C_8\text{-}C_{14})tricycloalkyl$, $-(C_5\text{-}C_{10})cycloalkenyl$, $-(C_8\text{-}C_{14})bicycloalkenyl$, $-(C_8\text{-}C_{14})tricycloalkenyl$, -(3- to 7-membered)heterocycle, or -(7- to 10-

membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups;

R_4 is -H, -(C_1-C_{10})alkyl, -C(O)R_9, or -C(O)NHR_9;

R_5 is -H or -(C_1-C_{10})alkyl;

each R_7 and R_8 is independently -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_{10})$_2$, -CH=NR_{10}, -NR_{10}OH, -OR_{10}, -COR$_{10}$, -C(O)OR_{10}, -OC(O)R_{10}, -OC(O)OR_{10}, -SR_{10}, -S(O)R_{10}, or -S(O)$_2$$R_{10}$;

each R_9 is -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -OH, -N(R_{10})$_2$, -CH=NR_{10}, -NR_{10}OH, -OR_{10}, or -SR_{10};

each R_{10} is independently -H, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5-C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

each R_{11} and R_{12} is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -N(R_7)$_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR$_7$, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$;

each R_{13} is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, CH_2(halo), or -halo;

each halo is independently -F, -Cl, -Br, or -I;

s is an integer ranging from 0 to 4;

o is an integer ranging from 0 to 4;

q is an integer ranging from 0 to 6;

r is an integer ranging from 0 to 5;

t is an integer ranging from 0 to 2;

p is an integer ranging from 0 to 2;

n is an integer ranging from 0 to 3; and

m is an integer ranging from 0 to 2.

A compound of formula (I)-(VII) or a pharmaceutically acceptable salt thereof (a "Hydroxyiminopiperazine Compound") is useful for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression (each being a "Condition") in an animal.

The invention also relates to compositions comprising an effective amount of a Hydroxyiminopiperazine Compound and a pharmaceutically acceptable carrier or excipient. The compositions are useful for treating or preventing a Condition in an animal.

The invention further relates to methods for treating a Condition, comprising administering to an animal in need thereof an effective amount of a Hydroxyiminopiperazine Compound.

The invention further relates to methods for preventing a Condition, comprising administering to an animal in need thereof an effective amount of a Hydroxyiminopiperazine Compound.

The invention still further relates to methods for inhibiting Vanilloid Receptor 1 ("VR1") function in a cell, comprising contacting a cell capable of expressing VR1 with an effective amount of a Hydroxyiminopiperazine Compound.

The invention still further relates to methods for inhibiting mGluR5 function in a cell, comprising contacting a cell capable of expressing mGluR5 with an effective amount of a Hydroxyiminopiperazine Compound.

The invention still further relates to methods for inhibiting metabotropic glutamate receptor 1 ("mGluR1") function in a cell, comprising contacting a cell capable of expressing mGluR1 with an effective amount of a Hydroxyiminopiperazine Compound.

The invention still further relates to a method for preparing a composition, comprising the step of admixing a Hydroxyiminopiperazine Compound and a pharmaceutically acceptable carrier or excipient.

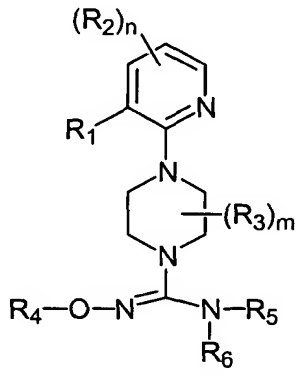
The invention still further relates to a kit comprising a container containing an effective amount of a Hydroxyiminopiperazine Compound.

The present invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

4. DETAILED DESCRIPTION OF THE INVENTION

4.1 THE HYDROXYIMINOPIPERAZINE COMPOUNDS OF FORMULA (I)

As stated above, the present invention encompasses compounds of Formula (I)



(I)

and pharmaceutically acceptable salts thereof, where R_1-R_6, n, and m are defined above for the Hydroxyiminopiperazine Compounds of formula (I).

In one embodiment, n is 0.

In another embodiment n is 1.

In another embodiment, n is 2.

In another embodiment, n is 3.

In another embodiment, n is an integer ranging from 0 to 3.

In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is -Cl.

In another embodiment, R_1 is -Br.

In another embodiment, R_1 is -I.

In another embodiment, R_1 is -F.

In another embodiment, R_1 is $-CH_3$.

In another embodiment, R_1 is $-NO_2$.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is $-OCH_3$.

In another embodiment, R_1 is $-NH_2$.

In another embodiment, R_1 is $-C(halo)_3$.

In another embodiment, R_1 is -CH(halo)$_2$.

In another embodiment, R_1 is -CH_2(halo).

In another embodiment, n is 1 and R_2 is -halo, -CN, -OH, NO_2, -O(C_1-C_6)alkyl, or -NH_2.

In another embodiment, n is 1 and R_2 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, n is 1 and R_2 is -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, m is 1 and R_3 is -halo, -CN, -OH, NO_2, -O(C_1-C_6)alkyl, or -NH_2.

In another embodiment, m is 1 and R_3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, m is 1 and R_3 is -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, m is 1 and R_3 is a -(C_1-C_{10})alkyl.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (S)-configuration.

In another embodiment, m is 1 and R_3 is methyl.

In another embodiment, m is 1, R_3 is methyl, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is methyl, and the carbon to which the R_3 group is attached is in the (S)-configuration.

In another embodiment, R_4 is -H.

In another embodiment, R_4 is -(C_1-C_{10})alkyl.

In another embodiment, R_4 is -C(O)R_9.

In another embodiment, R_4 is -C(O)NHR_9.

In another embodiment, R_5 is -H.

In another embodiment, R_5 is -(C_1-C_{10})alkyl.

In another embodiment, R_6 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 1-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, R_6 is -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment R_6 is -phenyl.

In another embodiment, n and m are 0, R_1 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6-phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n and m are 0, R_1 is -CF_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n and m are 0, R_1 is -Cl, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n and m are 0, R_1 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position

of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n and m are 0, R_1 is -CF_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n and m are 0, R_1 is -Cl, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n is 0, m is 1, R_1 is -CH_3, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6-phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n is 0, m is 1, R_1 is -CF_3, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n is 0, m is 1, R_1 is -Cl, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n is 0, m is 1, R_1 is $-CH_3$, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n is 0, m is 1, R_1 is $-CF_3$, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n is 0, m is 1, R_1 is -Cl, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, n and m are 0, R_1 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, n and m are 0, R_1 is $-CF_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, n and m are 0, R_1 is -Cl, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, n and m are 0, R_1 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, n and m are 0, R_1 is $-CF_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, n and m are 0, R_1 is -Cl, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, n is 0, m is 1, R_1 is $-CH_3$, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, n is 0, m is 1, R_1 is $-CF_3$, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, n is 0, m is 1, R_1 is -Cl, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

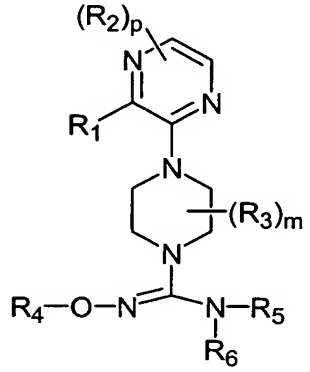
In another embodiment, n is 0, m is 1, R_1 is $-CH_3$, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, n is 0, m is 1, R_1 is $-CF_3$, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, n is 0, m is 1, R_1 is -Cl, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

4.2 THE HYDROXYIMINOPIPERAZINE COMPOUNDS OF FORMULA (II)

The present invention also encompasses compounds of formula (II):



(II)

and pharmaceutically acceptable salts thereof, where R_1-R_6, p, and m are defined above for the Hydroxyiminopiperazine Compounds of formula (II).

In one embodiment, p is 0.

In another embodiment p is 1.

In another embodiment, p is 2.

In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is -Cl.

In another embodiment, R_1 is -Br.

In another embodiment, R_1 is -I.

In another embodiment, R_1 is -F.

In another embodiment, R_1 is $-CH_3$.

In another embodiment, R_1 is $-NO_2$.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is $-OCH_3$.

In another embodiment, R_1 is $-NH_2$.

In another embodiment, R_1 is $-C(halo)_3$.

In another embodiment, R_1 is $-CH(halo)_2$.

In another embodiment, R_1 is $-CH_2(halo)$.

In another embodiment, p is 1 and R_2 is -halo, -CN, -OH, NO_2, $-O(C_1$-$C_6)$alkyl, or $-NH_2$.

In another embodiment, p is 1 and R_2 is $-(C_1$-$C_{10})$alkyl, $-(C_2$-$C_{10})$alkenyl, $-(C_2$-$C_{10})$alkynyl, $-(C_3$-$C_{10})$cycloalkyl, $-(C_8$-$C_{14})$bicycloalkyl, $-(C_8$-$C_{14})$tricycloalkyl, $-(C_5$-$C_{10})$cycloalkenyl, $-(C_8$-$C_{14})$bicycloalkenyl, $-(C_8$-$C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, p is 1 and R_2 is -phenyl, -naphthyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, m is 1 and R_3 is -halo, -CN, -OH, NO_2, $-O(C_1$-$C_6)$alkyl, or $-NH_2$.

In another embodiment, m is 1 and R_3 is $-(C_1$-$C_{10})$alkyl, $-(C_2$-$C_{10})$alkenyl, $-(C_2$-$C_{10})$alkynyl, $-(C_3$-$C_{10})$cycloalkyl, $-(C_8$-$C_{14})$bicycloalkyl, $-(C_8$-$C_{14})$tricycloalkyl, $-(C_5$-$C_{10})$cycloalkenyl, $-(C_8$-$C_{14})$bicycloalkenyl, $-(C_8$-$C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, m is 1 and R_3 is -phenyl, -naphthyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, m is 1 and R_3 is a $-(C_1$-$C_{10})$alkyl.

In another embodiment, m is 1, R_3 is a $-(C_1$-$C_{10})$alkyl, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is a $-(C_1$-$C_{10})$alkyl, and the carbon to which the R_3 group is attached is in the (S)-configuration.

In another embodiment, m is 1 and R_3 is $-CH_3$.

In another embodiment, m is 1, R_3 is $-CH_3$, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is $-CH_3$, and the carbon to which the R_3 group is attached is in the (S)-configuration.

In another embodiment, R_4 is -H.

In another embodiment, R_4 is $-(C_1\text{-}C_{10})$alkyl.

In another embodiment, R_4 is $-C(O)R_9$.

In another embodiment, R_4 is $-C(O)NHR_9$.

In another embodiment, R_5 is -H.

In another embodiment, R_5 is $-(C_1\text{-}C_{10})$alkyl.

In another embodiment, R_6 is $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_8\text{-}C_{14})$tricycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl,$-(C_8\text{-}C_{14})$bicycloalkenyl, $-(C_8\text{-}C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 1-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, R_6 is -phenyl, -naphthyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, R_6 is -phenyl.

In another embodiment, p and m are 0, R_1 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1\text{-}C_6)$ alkyl group. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is $-CF_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1\text{-}C_6)$ alkyl group. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1\text{-}C_6)$ alkyl group. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is substituted at the para-position of the R_6

-phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -CF_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -CH_3, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -CF_3, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -CH_3, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -CF_3, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p and m are 0, R_1 is -CF_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p and m are 0, R_1 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p and m are 0, R_1 is -CF_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p is 0, m is 1, R_1 is -CH_3, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p is 0, m is 1, R_1 is -CF_3, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

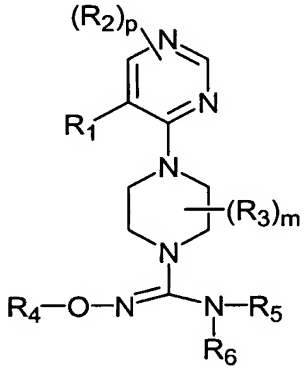
In another embodiment, p is 0, m is 1, R_1 is -CH_3, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p is 0, m is 1, R_1 is -CF_3, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

4.3 THE HYDROXYIMINOPIPERAZINE COMPOUNDS OF FORMULA (III)

The present invention also encompasses compounds of formula (III):



(III)

and pharmaceutically acceptable salts thereof, where R_1-R_6, p, and m are defined above for the Hydroxyiminopiperazine Compounds of formula (III).

In one embodiment, p is 0.

In another embodiment p is 1.

In another embodiment, p is 2.

In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is -Cl.

In another embodiment, R_1 is -Br.

In another embodiment, R_1 is -I.

In another embodiment, R_1 is -F.

In another embodiment, R_1 is $-CH_3$.

In another embodiment, R_1 is $-NO_2$.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is $-OCH_3$.

In another embodiment, R_1 is $-NH_2$.

In another embodiment, R_1 is $-C(halo)_3$.

In another embodiment, R_1 is $-CH(halo)_2$.

In another embodiment, R_1 is $-CH_2(halo)$.

In another embodiment, p is 1 and R_2 is -halo, -CN, -OH, NO_2, $-O(C_1$-$C_6)$alkyl, or $-NH_2$.

In another embodiment, p is 1 and R_2 is $-(C_1$-$C_{10})$alkyl, $-(C_2$-$C_{10})$alkenyl, $-(C_2$-$C_{10})$alkynyl, $-(C_3$-$C_{10})$cycloalkyl, $-(C_8$-$C_{14})$bicycloalkyl, $-(C_8$-$C_{14})$tricycloalkyl, $-(C_5$-$C_{10})$cycloalkenyl, $-(C_8$-$C_{14})$bicycloalkenyl, $-(C_8$-$C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, p is 1 and R_2 is -phenyl, -naphthyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, m is 1 and R_3 is -halo, -CN, -OH, NO_2, $-O(C_1$-$C_6)$alkyl, or $-NH_2$.

In another embodiment, m is 1 and R_3 is $-(C_1$-$C_{10})$alkyl, $-(C_2$-$C_{10})$alkenyl, $-(C_2$-$C_{10})$alkynyl, $-(C_3$-$C_{10})$cycloalkyl, $-(C_8$-$C_{14})$bicycloalkyl, $-(C_8$-$C_{14})$tricycloalkyl, $-(C_5$-$C_{10})$cycloalkenyl, $-(C_8$-$C_{14})$bicycloalkenyl, $-(C_8$-$C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, m is 1 and R_3 is -phenyl, -naphthyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, m is 1 and R_3 is a $-(C_1$-$C_{10})$alkyl.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (S)-configuration.

In another embodiment, m is 1 and R_3 is -CH_3.

In another embodiment, m is 1, R_3 is -CH_3, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is -CH_3, and the carbon to which the R_3 group is attached is in the (S)-configuration.

In another embodiment, R_4 is -H.

In another embodiment, R_4 is -(C_1-C_{10})alkyl.

In another embodiment, R_4 is -C(O)R_9.

In another embodiment, R_4 is -C(O)NHR_9.

In another embodiment, R_5 is -H.

In another embodiment, R_5 is -(C_1-C_{10})alkyl.

In another embodiment, R_6 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 1-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, R_6 is -phenyl.

In another embodiment, R_6 is -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, p and m are 0, R_1 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -CF_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group

substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6-phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -CF_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -CH_3, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -CF_3, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the -phenyl is substituted with a -(C_1-C_6)

alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -CH_3, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -CF_3, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p and m are 0, R_1 is -CF_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p and m are 0, R_1 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p and m are 0, R_1 is $-CF_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p is 0, m is 1, R_1 is $-CH_3$, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p is 0, m is 1, R_1 is $-CF_3$, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

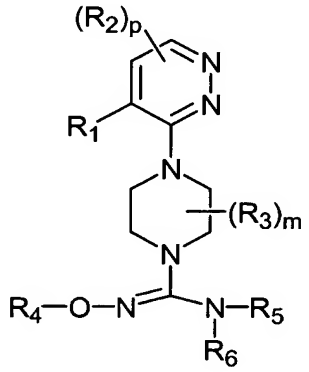
In another embodiment, p is 0, m is 1, R_1 is $-CH_3$, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p is 0, m is 1, R_1 is $-CF_3$, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

4.4 THE HYDROXYIMINOPIPERAZINE COMPOUNDS OF FORMULA (IV)

The present invention also encompasses compounds of formula (IV):



(IV)

and pharmaceutically acceptable salts thereof, where R_1-R_6, p, and m are defined above for the Hydroxyiminopiperazine Compounds of formula (IV).

In one embodiment, p is 0.

In another embodiment p is 1.

In another embodiment, p is 2.

In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is -Cl.

In another embodiment, R_1 is -Br.

In another embodiment, R_1 is -I.

In another embodiment, R_1 is -F.

In another embodiment, R_1 is $-CH_3$.

In another embodiment, R_1 is $-NO_2$.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is $-OCH_3$.

In another embodiment, R_1 is $-NH_2$.

In another embodiment, R_1 is $-C(halo)_3$.

In another embodiment, R_1 is $-CH(halo)_2$.

In another embodiment, R_1 is $-CH_2(halo)$.

In another embodiment, p is 1 and R_2 is -halo, -CN, -OH, NO_2, $-O(C_1$-$C_6)$alkyl, or $-NH_2$.

In another embodiment, p is 1 and R_2 is $-(C_1$-$C_{10})$alkyl, $-(C_2$-$C_{10})$alkenyl, $-(C_2$-$C_{10})$alkynyl, $-(C_3$-$C_{10})$cycloalkyl, $-(C_8$-$C_{14})$bicycloalkyl, $-(C_8$-$C_{14})$tricycloalkyl, $-(C_5$-$C_{10})$cycloalkenyl, $-(C_8$-$C_{14})$bicycloalkenyl, $-(C_8$-$C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, p is 1 and R_2 is -phenyl, -naphthyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, m is 1 and R_3 is -halo, -CN, -OH, NO_2, $-O(C_1$-$C_6)$alkyl, or $-NH_2$.

In another embodiment, m is 1 and R_3 is $-(C_1$-$C_{10})$alkyl, $-(C_2$-$C_{10})$alkenyl, $-(C_2$-$C_{10})$alkynyl, $-(C_3$-$C_{10})$cycloalkyl, $-(C_8$-$C_{14})$bicycloalkyl, $-(C_8$-$C_{14})$tricycloalkyl, $-(C_5$-$C_{10})$cycloalkenyl, $-(C_8$-$C_{14})$bicycloalkenyl, $-(C_8$-$C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, m is 1 and R_3 is -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, m is 1 and R_3 is a -(C_1-C_{10})alkyl.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (S)-configuration.

In another embodiment, m is 1 and R_3 is -CH_3.

In another embodiment, m is 1, R_3 is -CH_3, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is -CH_3, and the carbon to which the R_3 group is attached is in the (S)-configuration.

In another embodiment, R_4 is -H.

In another embodiment, R_4 is -(C_1-C_{10})alkyl.

In another embodiment, R_4 is -C(O)R_9.

In another embodiment, R_4 is -C(O)NHR_9.

In another embodiment, R_5 is -H.

In another embodiment, R_5 is -(C_1-C_{10})alkyl.

In another embodiment, R_6 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 1-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, R_6 is -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, R_6 is -phenyl.

In one embodiment, p and m are 0, R_1 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is $-CF_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is $-CF_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is $-CH_3$, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl

group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -CF_3, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -CH_3, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -CF_3, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, p and m are 0, R_1 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, p and m are 0, R_1 is $-CF_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p and m are 0, R_1 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p and m are 0, R_1 is $-CF_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p and m are 0, R_1 is -Cl, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p is 0, m is 1, R_1 is $-CH_3$, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p is 0, m is 1, R_1 is $-CF_3$, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

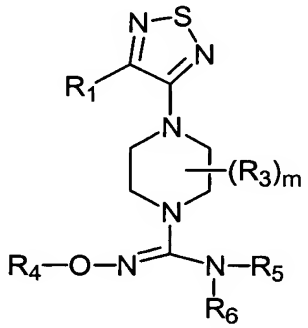
In another embodiment, p is 0, m is 1, R_1 is $-CH_3$, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p is 0, m is 1, R_1 is $-CF_3$, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, p is 0, m is 1, R_1 is -Cl, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

4.5 THE HYDROXYIMINOPIPERAZINE COMPOUNDS OF FORMULA (V)

The present invention also encompasses compounds of formula (V):



(V)

and pharmaceutically acceptable salts thereof, where R_1, R_3-R_6, and m are defined above for

the Hydroxyiminopiperazine Compounds of formula (V).

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is -Cl.

In another embodiment, R_1 is -Br.

In another embodiment, R_1 is -I.

In another embodiment, R_1 is -F.

In another embodiment, R_1 is $-CH_3$.

In another embodiment, R_1 is $-NO_2$.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is $-OCH_3$.

In another embodiment, R_1 is $-NH_2$.

In another embodiment, R_1 is $-C(halo)_3$.

In another embodiment, R_1 is $-CH(halo)_2$.

In another embodiment, R_1 is $-CH_2(halo)$.

In another embodiment, m is 1 and R_3 is -halo, -CN, -OH, NO_2, or $-NH_2$.

In another embodiment, m is 1 and R_3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, m is 1 and R_3 is -phenyl, -naphthyl, -(C_{14})aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, m is 1 and R_3 is a -(C_1-C_{10})alkyl.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (S)-configuration.

In another embodiment, m is 1 and R_3 is $-CH_3$.

In another embodiment, m is 1, R_3 is $-CH_3$, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is $-CH_3$, and the carbon to which the R_3 group is attached is in the (S)-configuration.

In another embodiment, R_4 is -H.

In another embodiment, R_4 is $-(C_1\text{-}C_{10})$alkyl.

In another embodiment, R_4 is $-C(O)R_9$.

In another embodiment, R_4 is $-C(O)NHR_9$.

In another embodiment, R_5 is -H.

In another embodiment, R_5 is $-(C_1\text{-}C_{10})$alkyl.

In another embodiment, R_6 is $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_8\text{-}C_{14})$tricycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl,$-(C_8\text{-}C_{14})$bicycloalkenyl, $-(C_8\text{-}C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 1-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_7 groups.

In another embodiment, R_6 is -phenyl, -naphthyl, $-(C_{14})$aryl, or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_8 groups.

In another embodiment, R_6 is -phenyl.

In another embodiment, m is 0, R_1 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1\text{-}C_6)$ alkyl group. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 0, R_1 is $-CF_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1\text{-}C_6)$ alkyl group. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 0, R_1 is -Cl, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a $-(C_1\text{-}C_6)$ alkyl group. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the $-(C_1\text{-}C_6)$ alkyl group is a *t*-butyl group substituted at

the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 0, R_1 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 0, R_1 is -CF_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 0, R_1 is -Cl, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 1, R_1 is -CH_3, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 1, R_1 is -CF_3, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 1, R_1 is -Cl, R_3 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl

group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 1, R_1 is -CH_3, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 1, R_1 is -CF_3, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 1, R_1 is -Cl, R_3 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl. In another embodiment, the R_6 -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at the para-position of the R_6 -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the para-position of the R_6 -phenyl.

In another embodiment, m is 0, R_1 is -CH_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, m is 0, R_1 is -CF_3, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, m is 0, R_1 is -Cl, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, m is 0, R_1 is -CH_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, m is 0, R_1 is -CF_3, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, m is 0, R_1 is -Cl, R_4 is -CH_3, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a -CF_3.

In another embodiment, m is 1, R_1 is $-CH_3$, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, m is 1, R_1 is $-CF_3$, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, m is 1, R_1 is -Cl, R_3 is $-CH_3$, R_4 is -H, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

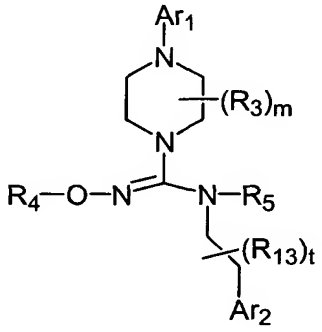
In another embodiment, m is 1, R_1 is $-CH_3$, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, m is 1, R_1 is $-CF_3$, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

In another embodiment, m is 1, R_1 is -Cl, R_3 is $-CH_3$, R_4 is $-CH_3$, R_5 is -H, and R_6 is -phenyl substituted at its para-position with a $-CF_3$.

4.6 THE HYDROXYIMINOPIPERAZINE COMPOUNDS OF FORMULA (VI)

The present invention also encompasses compounds of formula (VI):



(VI)

and pharmaceutically acceptable salts thereof, where Ar_1, Ar_2, R_3-R_5, R_{13}, m and t are defined above for the Hydroxyiminopiperazine Compounds of formula (VI).

In one embodiment Ar_1 is a pyridyl group.

In another embodiment, Ar_1 is a pyrimidinyl group.

In another embodiment, Ar_1 is a pyridazinyl group.

In another embodiment, Ar_1 is a pyrazinyl group.

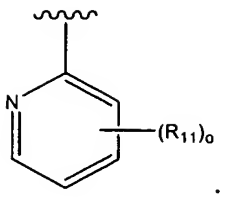
In another embodiment, Ar_1 is a thiadiazolyl group.

In another embodiment, Ar_2 is a benzothiazolyl group.

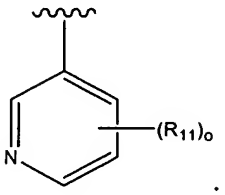
In another embodiment, Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_2 is a benzooxazolyl group.

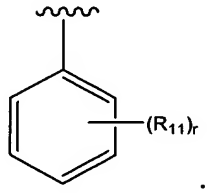
In another embodiment, Ar_2 is



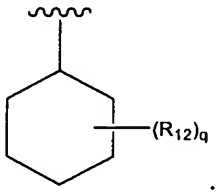
In another embodiment, Ar_2 is



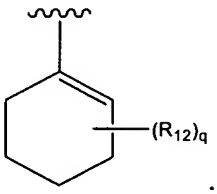
In another embodiment, Ar_2 is



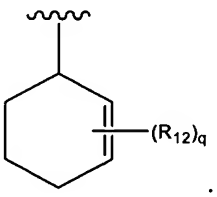
In another embodiment, Ar_2 is



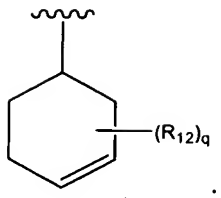
In another embodiment, Ar_2 is



In another embodiment, Ar_2 is



In another embodiment, Ar_2 is



In another embodiment, R_1 is -H.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is -Cl.

In another embodiment, R_1 is -Br.

In another embodiment, R_1 is -I.

In another embodiment, R_1 is -F.

In another embodiment, R_1 is $-CH_3$.

In another embodiment, R_1 is $-NO_2$.

In another embodiment, R_1 is -CN.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is $-OCH_3$.

In another embodiment, R_1 is $-NH_2$.

In another embodiment, R_1 is $-C(halo)_3$.

In another embodiment, R_1 is $-CH(halo)_2$.

In another embodiment, R_1 is $-CH_2(halo)$.

In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, n is 0.

In another embodiment, n is 1.

In another embodiment, n is 2.

In another embodiment, n is 3.

In another embodiment, p is 0.

In another embodiment, p is 1.

In another embodiment, p is 2.

In another embodiment, t is 0.

In another embodiment, t is 1.

In another embodiment, t is 2.

In another embodiment, s is 0.

In another embodiment, s is 1.

In another embodiment, s is 2.

In another embodiment, s is 3.

In another embodiment, s is 4.

In another embodiment, o is 0.

In another embodiment, o is 1.

In another embodiment, o is 2.

In another embodiment, o is 3.

In another embodiment, o is 4.

In another embodiment, q is 0.

In another embodiment, q is 1.

In another embodiment, q is 2.

In another embodiment, q is 3.

In another embodiment, q is 4.

In another embodiment, q is 5.

In another embodiment, q is 6.

In another embodiment, r is 0.

In another embodiment, r is 1.

In another embodiment, r is 2.

In another embodiment, r is 3.

In another embodiment, r is 4.

In another embodiment, r is 5.

In another embodiment, n or p is 1 and R_2 is -halo, -CN, -OH, -NO_2, or -NH_2.

In another embodiment, n or p is 1 and R_2 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, n or p is 1 and R_2 is -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, m is 1 and R_3 is -halo, -CN, -OH, -NO_2, or -NH_2.

In another embodiment, m is 1 and R_3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-

C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, m is 1 and R_3 is -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered) heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, m is 1 and R_3 is a -(C_1-C_{10})alkyl.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (S)-configuration.

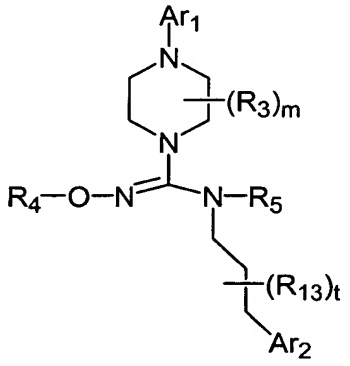
In another embodiment, m is 1 and R_3 is -CH_3.

In another embodiment, m is 1, R_3 is -CH_3, and the carbon atom to which the R_3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is -CH_3, and the carbon atom to which the R_3 is attached is in the (S)-configuration.

4.7 THE HYDROXYIMINOPIPERAZINE COMPOUNDS OF FORMULA (VII)

The present invention also encompasses compounds of formula (VII):



(VII)

and pharmaceutically acceptable salts thereof, where Ar_1, Ar_2, R_3-R_5, R_{13}, m and t are defined above for the Hydroxyiminopiperazine Compounds of formula (VII).

In one embodiment Ar_1 is a pyridyl group.

In another embodiment, Ar_1 is a pyrimidinyl group.

In another embodiment, Ar_1 is a pyridazinyl group.

In another embodiment, Ar_1 is a pyrazinyl group.

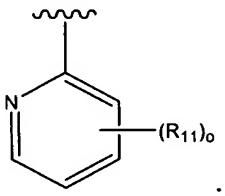
In another embodiment, Ar_1 is a thiadiazolyl group.

In another embodiment, Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_2 is a benzoimidazolyl group.

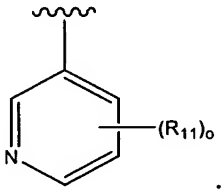
In another embodiment, Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_2 is



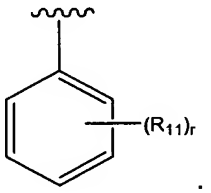
.

In another embodiment, Ar_2 is



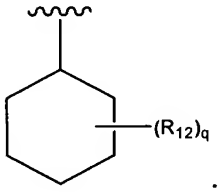
.

In another embodiment, Ar_2 is



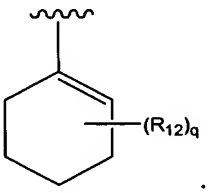
.

In another embodiment, Ar_2 is



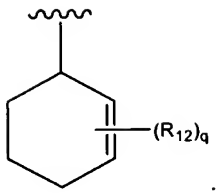
.

In another embodiment, Ar_2 is

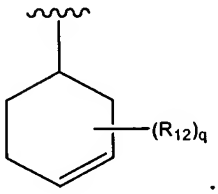


.

In another embodiment, Ar_2 is



In another embodiment, Ar_2 is



In another embodiment, R_1 is -H.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is -Cl.

In another embodiment, R_1 is -Br.

In another embodiment, R_1 is -I.

In another embodiment, R_1 is -F.

In another embodiment, R_1 is $-CH_3$.

In another embodiment, R_1 is $-NO_2$.

In another embodiment, R_1 is -CN.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is $-OCH_3$.

In another embodiment, R_1 is $-NH_2$.

In another embodiment, R_1 is $-C(halo)_3$.

In another embodiment, R_1 is $-CH(halo)_2$.

In another embodiment, R_1 is $-CH_2(halo)$.

In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, n is 0.

In another embodiment, n is 1.

In another embodiment, n is 2.

In another embodiment, n is 3.

In another embodiment, p is 0.

In another embodiment, p is 1.

In another embodiment, p is 2.

In another embodiment, t is 0.

In another embodiment, t is 1.

In another embodiment, t is 2.

In another embodiment, s is 0.

In another embodiment, s is 1.

In another embodiment, s is 2.

In another embodiment, s is 3.

In another embodiment, s is 4.

In another embodiment, o is 0.

In another embodiment, o is 1.

In another embodiment, o is 2.

In another embodiment, o is 3.

In another embodiment, o is 4.

In another embodiment, q is 0.

In another embodiment, q is 1.

In another embodiment, q is 2.

In another embodiment, q is 3.

In another embodiment, q is 4.

In another embodiment, q is 5.

In another embodiment, q is 6.

In another embodiment, r is 0.

In another embodiment, r is 1.

In another embodiment, r is 2.

In another embodiment, r is 3.

In another embodiment, r is 4.

In another embodiment, r is 5.

In another embodiment, n or p is 1 and R_2 is -halo, -CN, -OH, -NO_2, or -NH_2.

In another embodiment, n or p is 1 and R_2 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, n or p is 1 and R_2 is -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, m is 1 and R_3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, m is 1 and R_3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, m is 1 and R_3 is -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered) heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, m is 1 and R_3 is a -(C_1-C_{10})alkyl.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is a -(C_1-C_{10})alkyl, and the carbon to which the R_3 group is attached is in the (S)-configuration.

In another embodiment, m is 1 and R_3 is $-CH_3$.

In another embodiment, m is 1, R_3 is $-CH_3$, and the carbon atom to which the R_3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is $-CH_3$, and the carbon atom to which the R_3 is attached is in the (S)-configuration.

4.8 THE HYDROXYIMINOPIPERAZINE COMPOUNDS OF FORMULA (I-VII)

In the Hydroxyiminopiperazine Compounds each R_3 can be on any carbon of the piperazine ring. In one embodiment, the Hydroxyiminopiperazine Compounds have only one R_3 group, and that R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group, and that R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group.

In another embodiment, two R_3 groups are on the same carbon atom of the piperazine ring.

In another embodiment, a first R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group and a second R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group.

In another embodiment, the Hydroxyiminopiperazine Compound has two R_3 groups, each being attached to a different carbon atom adjacent to the nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group. In another embodiment, the Hydroxyiminopiperazine Compound has two R_3 groups, each being attached to a different carbon atom adjacent to the nitrogen atom attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group.

In another embodiment, wherein the Hydroxyiminopiperazine Compound has one or two R_3 groups, the carbon atom to which an R_3 group is attached has the (R) configuration. In another embodiment, wherein the Hydroxyiminopiperazine Compound has one or two R_3 groups, the carbon atom to which the R_3 group is attached has the (S) configuration. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups, and at least one of the carbon atoms to which an R_3 group is attached has the (R) configuration. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups, and at least one of the carbon atoms to which an R_3 group is attached has the (S) configuration.

In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; and the carbon to which the R_3 group is attached is in the (R) configuration. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is -CH_3. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3

groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is $-CF_3$. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is $-CH_2CH_3$.

In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the $-C(=N-OR_4)-N(R_5)(R_6)$, $-C(=N-OR_4)-N(R_5)$-phenethyl group, or $-C(=N-OR_4)-N(R_5)$-phenpropyl group; and the carbon to which the R_3 group is attached is in the (R) configuration. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the $-C(=N-OR_4)-N(R_5)(R_6)$, $-C(=N-OR_4)-N(R_5)$-phenethyl group, or $-C(=N-OR_4)-N(R_5)$-phenpropyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is $-(C_1-C_4)$alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the $-C(=N-OR_4)-N(R_5)(R_6)$, $-C(=N-OR_4)-N(R_5)$-phenethyl group, or $-C(=N-OR_4)-N(R_5)$-phenpropyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is $-CH_3$. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the $-C(=N-OR_4)-N(R_5)(R_6)$, $-C(=N-OR_4)-N(R_5)$-phenethyl group; or $-C(=N-OR_4)-N(R_5)$-phenpropyl group; the carbon to which the R_3 group is attached is in the (R) configuration, and R_3 is $-CF_3$. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the $-C(=N-OR_4)-N(R_5)(R_6)$, $-C(=N-OR_4)-N(R_5)$-phenethyl group, or $-C(=N-OR_4)-N(R_5)$-phenpropyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is $-CH_2CH_3$.

In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; and the carbon to which the R_3 group is attached is in the (S) configuration. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3

group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is $-CH_3$. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is $-CF_3$. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is $-CH_2CH_3$.

In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group; and the carbon to which the R_3 group is attached is in the (S) configuration. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group or -C(=N-OR_4)-N(R_5)-phenpropyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is $-CH_3$. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is $-CF_3$. In another embodiment, the Hydroxyiminopiperazine Compound has one or two R_3 groups; an R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-

$N(R_5)(R_6)$, -C(=N-OR_4)-$N(R_5)$-phenethyl group, or -C(=N-OR_4)-$N(R_5)$-phenpropyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is $-CH_2CH_3$.

In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; and the carbon to which the R_3 group is attached is in the (R) configuration. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is $-CH_3$. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is $-CF_3$. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is $-CH_2CH_3$.

In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the -C(=N-OR_4)-$N(R_5)(R_6)$, -C(=N-OR_4)-$N(R_5)$-phenethyl group, or -C(=N-OR_4)-NR_5-phenpropyl group; and the carbon to which the R_3 group is attached is in the (R) configuration. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-$N(R_5)(R_6)$, -C(=N-OR_4)-$N(R_5)$-phenethyl group, or -C(=N-OR_4)-$N(R_5)$-phenpropyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-$N(R_5)(R_6)$, -C(=N-OR_4)-$N(R_5)$-phenethyl group, or -C(=N-OR_4)-$N(R_5)$-phenpropyl group;

the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is $-CH_3$. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the $-C(=N-OR_4)-N(R_5)(R_6)$, $-C(=N-OR_4)-N(R_5)$-phenethyl group, or $-C(=N-OR_4)-N(R_5)$-phenpropyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is $-CF_3$. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the $-C(=N-OR_4)-N(R_5)(R_6)$, $-C(=N-OR_4)-N(R_5)$-phenethyl group, or $-C(=N-OR_4)-N(R_5)$-phenpropyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is $-CH_2CH_3$.

In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; and the carbon to which the R_3 group is attached is in the (S) configuration. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is $-(C_1-C_4)$alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is $-CH_3$. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is $-CF_3$. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and $R_3$is $-CH_2CH_3$.

In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the $-C(=N-OR_4)-N(R_5)(R_6)$, $-C(=N-OR_4)-N(R_5)$-phenethyl group, or $-C(=N-OR_4)-N(R_5)$-phenpropyl group; and the carbon to which the R_3 group is attached is in the (S) configuration. In another embodiment, the Hydroxyiminopiperazine Compound has

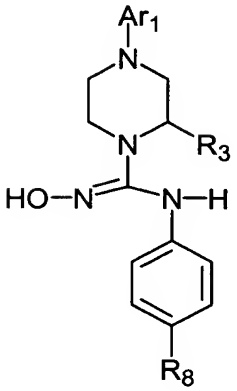
only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is -CH_3. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group; the carbon to which the R_3 group is attached is in the (S) configuration; and R_3 is -CF_3. In another embodiment, the Hydroxyiminopiperazine Compound has only one R_3 group; the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and R_3 is -CH_2CH_3.

In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl, or -C(=N-OR_4)-NR_5-phenpropyl group. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl, or -C(=N-OR_4)-NR_5-phenpropyl group and the R_3 group is a -CH_3. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group and the R_3 group is a -CF_3. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group and the R_3 group is a -CH_2CH_3. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group and the carbon to which the R_3 group is attached is in the (R) configuration. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and the R_3 group is a -CH_3. In

another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and the R_3 group is a -CF_3. In another embodiment, the R_3 group is attached to a carbon atom adjacent to the nitrogen attached to the -C(=N-OR_4)-N(R_5)(R_6), -C(=N-OR_4)-N(R_5)-phenethyl group, or -C(=N-OR_4)-N(R_5)-phenpropyl group; the carbon to which the R_3 group is attached is in the (R) configuration; and the R_3 group is a -CH_2CH_3.

Illustrative Hydroxyiminopiperazine Compounds are listed below in Tables I-VII:

Table I



and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar_1	R_8
A1 (a, b, c, and d)	-2-(3-chloropyridyl)	-t-butyl
A2 (a, b, c, and d)	-2-(3-chloropyridyl)	-iso-butyl
A3 (a, b, c, and d)	-2-(3-chloropyridyl)	-sec-butyl
A4 (a, b, c, and d)	-2-(3-chloropyridyl)	-cyclohexyl
A5 (a, b, c, and d)	-2-(3-chloropyridyl)	-t-butoxy
A6 (a, b, c, and d)	-2-(3-chloropyridyl)	-isopropoxy
A7 (a, b, c, and d)	-2-(3-chloropyridyl)	$-CF_3$
A8 (a, b, c, and d)	-2-(3-chloropyridyl)	$-OCF_3$
A9 (a, b, c, and d)	-2-(3-chloropyridyl)	-Cl
A10 (a, b, c, and d)	-2-(3-chloropyridyl)	-Br
A11 (a, b, c, and d)	-2-(3-chloropyridyl)	-I
A12 (a, b, c, and d)	-2-(3-chloropyridyl)	-n-butyl
A13 (a, b, c, and d)	-2-(3-chloropyridyl)	-n-propyl
A14 (a, b, c, and d)	-2-(3-chloropyridyl)	-iso-propyl
A15 (a, b, c, and d)	-2-(3-fluoropyridyl)	-t-butyl
A16 (a, b, c, and d)	-2-(3-fluoropyridyl)	-iso-butyl
A17 (a, b, c, and d)	-2-(3-fluoropyridyl)	-sec-butyl
A18 (a, b, c, and d)	-2-(3-fluoropyridyl)	-cyclohexyl
A19 (a, b, c, and d)	-2-(3-fluoropyridyl)	-t-butoxy
A20 (a, b, c, and d)	-2-(3-fluoropyridyl)	-isopropoxy
A21 (a, b, c, and d)	-2-(3-fluoropyridyl)	$-CF_3$

A22 (a, b, c, and d)	-2-(3-fluoropyridyl)	-OCF_3
A23 (a, b, c, and d)	-2-(3-fluoropyridyl)	-Cl
A24 (a, b, c, and d)	-2-(3-fluoropyridyl)	-Br
A25 (a, b, c, and d)	-2-(3-fluoropyridyl)	-I
A26 (a, b, c, and d)	-2-(3-fluoropyridyl)	-n-butyl
A27 (a, b, c, and d)	-2-(3-fluoropyridyl)	-n-propyl
A28 (a, b, c, and d)	-2-(3-fluoropyridyl)	-iso-propyl
A29 (a, b, c, and d)	-2-(3-methylpyridyl)	-t-butyl
A30 (a, b, c, and d)	-2-(3-methylpyridyl)	-iso-butyl
A31 (a, b, c, and d)	-2-(3-methylpyridyl)	-sec-butyl
A32 (a, b, c, and d)	-2-(3-methylpyridyl)	-cyclohexyl
A33 (a, b, c, and d)	-2-(3-methylpyridyl)	-t-butoxy
A34 (a, b, c, and d)	-2-(3-methylpyridyl)	-isopropoxy
A35 (a, b, c, and d)	-2-(3-methylpyridyl)	-CF_3
A36 (a, b, c, and d)	-2-(3-methylpyridyl)	-OCF_3
A37 (a, b, c, and d)	-2-(3-methylpyridyl)	-Cl
A38 (a, b, c, and d)	-2-(3-methylpyridyl)	-Br
A39 (a, b, c, and d)	-2-(3-methylpyridyl)	-I
A40 (a, b, c, and d)	-2-(3-methylpyridyl)	-n-butyl
A41 (a, b, c, and d)	-2-(3-methylpyridyl)	-n-propyl
A42 (a, b, c, and d)	-2-(3-methylpyridyl)	-iso-propyl
A43 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-t-butyl
A44 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-iso-butyl
A45 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-sec-butyl
A46 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-cyclohexyl
A47 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-t-butoxy
A48 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-isopropoxy
A49 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-CF_3
A50 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-OCF_3
A51 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-Cl
A52 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-Br
A53 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-I
A54 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-n-butyl
A55 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-n-propyl
A56 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-iso-propyl

A57 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-t-butyl
A58 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-iso-butyl
A59 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-sec-butyl
A60 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-cyclohexyl
A61 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-t-butoxy
A62 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-isopropoxy
A63 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-CF_3
A64 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-OCF_3
A65 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-Cl
A66 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-Br
A67 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-I
A68 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-n-butyl
A69 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-n-propyl
A70 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-iso-propyl
A71 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-t-butyl
A72 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-iso-butyl
A73 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-sec-butyl
A74 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-cyclohexyl
A75 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-t-butoxy
A76 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-isopropoxy
A77 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-CF_3
A78 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-OCF_3
A79 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-Cl
A80 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-Br
A81 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-I
A82 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-n-butyl
A83 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-n-propyl
A84 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-iso-propyl
A85 (a, b, c, and d)	-2-(3-nitropyridyl)	-t-butyl
A86 (a, b, c, and d)	-2-(3-nitropyridyl)	-iso-butyl
A87 (a, b, c, and d)	-2-(3-nitropyridyl)	-sec-butyl
A88 (a, b, c, and d)	-2-(3-nitropyridyl)	-cyclohexyl
A89 (a, b, c, and d)	-2-(3-nitropyridyl)	-t-butoxy
A90 (a, b, c, and d)	-2-(3-nitropyridyl)	-isopropoxy
A91 (a, b, c, and d)	-2-(3-nitropyridyl)	-CF_3

A92 (a, b, c, and d)	-2-(3-nitropyridyl)	-OCF_3
A93 (a, b, c, and d)	-2-(3-nitropyridyl)	-Cl
A94 (a, b, c, and d)	-2-(3-nitropyridyl)	-Br
A95 (a, b, c, and d)	-2-(3-nitropyridyl)	-I
A96 (a, b, c, and d)	-2-(3-nitropyridyl)	-n-butyl
A97 (a, b, c, and d)	-2-(3-nitropyridyl)	-n-propyl
A98 (a, b, c, and d)	-2-(3-nitropyridyl)	-iso-propyl
A99 (a, b, c, and d)	-2-(3-cyanopyridyl)	-t-butyl
A100 (a, b, c, and d)	-2-(3-cyanopyridyl)	-iso-butyl
A101 (a, b, c, and d)	-2-(3-cyanopyridyl)	-sec-butyl
A102 (a, b, c, and d)	-2-(3-cyanopyridyl)	-cyclohexyl
A103 (a, b, c, and d)	-2-(3-cyanopyridyl)	-t-butoxy
A104 (a, b, c, and d)	-2-(3-cyanopyridyl)	-isopropoxy
A105 (a, b, c, and d)	-2-(3-cyanopyridyl)	-CF_3
A106 (a, b, c, and d)	-2-(3-cyanopyridyl)	-OCF_3
A107 (a, b, c, and d)	-2-(3-cyanopyridyl)	-Cl
A108 (a, b, c, and d)	-2-(3-cyanopyridyl)	-Br
A109 (a, b, c, and d)	-2-(3-cyanopyridyl)	-I
A110 (a, b, c, and d)	-2-(3-cyanopyridyl)	-n-butyl
A111 (a, b, c, and d)	-2-(3-cyanopyridyl)	-n-propyl
A112 (a, b, c, and d)	-2-(3-cyanopyridyl)	-isopropyl
A113 (a, b, c, and d)	-2-(3-bromopyridyl)	-t-butyl
A114 (a, b, c, and d)	-2-(3-bromopyridyl)	-iso-butyl
A115 (a, b, c, and d)	-2-(3-bromopyridyl)	-sec-butyl
A116 (a, b, c, and d)	-2-(3-bromopyridyl)	-cyclohexyl
A117 (a, b, c, and d)	-2-(3-bromopyridyl)	-t-butoxy
A118 (a, b, c, and d)	-2-(3-bromopyridyl)	-isopropoxy
A119 (a, b, c, and d)	-2-(3-bromopyridyl)	-CF_3
A120 (a, b, c, and d)	-2-(3-bromopyridyl)	-OCF_3
A121 (a, b, c, and d)	-2-(3-bromopyridyl)	-Cl
A122 (a, b, c, and d)	-2-(3-bromopyridyl)	-Br
A123 (a, b, c, and d)	-2-(3-bromopyridyl)	-I
A124 (a, b, c, and d)	-2-(3-bromopyridyl)	-n-butyl
A125 (a, b, c, and d)	-2-(3-bromopyridyl)	-n-propyl
A126 (a, b, c, and d)	-2-(3-bromopyridyl)	-iso-propyl

A127 (a, b, c, and d)	-2-(3-iodopyridyl)	-t-butyl
A128 (a, b, c, and d)	-2-(3-iodopyridyl)	-iso-butyl
A129 (a, b, c, and d)	-2-(3-iodopyridyl)	-sec-butyl
A130 (a, b, c, and d)	-2-(3-iodopyridyl)	-cyclohexyl
A131 (a, b, c, and d)	-2-(3-iodopyridyl)	-t-butoxy
A132 (a, b, c, and d)	-2-(3-iodopyridyl)	-isopropoxy
A133 (a, b, c, and d)	-2-(3-iodopyridyl)	$-CF_3$
A134 (a, b, c, and d)	-2-(3-iodopyridyl)	$-OCF_3$
A135 (a, b, c, and d)	-2-(3-iodopyridyl)	-Cl
A136 (a, b, c, and d)	-2-(3-iodopyridyl)	-Br
A137 (a, b, c, and d)	-2-(3-iodopyridyl)	-I
A138 (a, b, c, and d)	-2-(3-iodopyridyl)	-n-butyl
A139 (a, b, c, and d)	-2-(3-iodopyridyl)	-n-propyl
A140 (a, b, c, and d)	-2-(3-iodopyridyl)	-iso-propyl
A141 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-t-butyl
A142 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-iso-butyl
A143 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-sec-butyl
A144 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-cyclohexyl
A145 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-t-butoxy
A146 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-isopropoxy
A147 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	$-CF_3$
A148 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	$-OCF_3$
A149 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-Cl
A150 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-Br
A151 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-I
A152 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-n-butyl
A153 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-n-propyl
A154 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-iso-propyl
A155 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-t-butyl
A156 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-iso-butyl
A157 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-sec-butyl
A158 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-cyclohexyl
A159 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-t-butoxy
A160 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-isopropoxy
A161 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	$-CF_3$

A162 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-OCF_3
A163 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-Cl
A164 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-Br
A165 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-I
A166 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-n-butyl
A167 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-n-propyl
A168 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-iso-propyl
A169 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-t-butyl
A170 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-iso-butyl
A171 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-sec-butyl
A172 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-cyclohexyl
A173 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-t-butoxy
A174 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-isopropoxy
A175 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-CF_3
A176 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-OCF_3
A177 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-Cl
A178 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-Br
A179 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-I
A180 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-n-butyl
A181 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-n-propyl
A182 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-iso-propyl
A183 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-t-butyl
A184 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-iso-butyl
A185 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-sec-butyl
A186 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-cyclohexyl
A187 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-t-butoxy
A188 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-isopropoxy
A189 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-CF_3
A190 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-OCF_3
A191 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-Cl
A192 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-Br
A193 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-I
A194 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-n-butyl
A195 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-n-propyl
A196 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-iso-propyl

A197 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-t-butyl
A198 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-iso-butyl
A199 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-sec-butyl
A200 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-cyclohexyl
A201 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-t-butoxy
A202 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-isopropoxy
A203 (a, b, c, and d)	-2-(3-methylpyrazinyl)	$-CF_3$
A204 (a, b, c, and d)	-2-(3-methylpyrazinyl)	$-OCF_3$
A205 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-Cl
A206 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-Br
A207 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-I
A208 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-n-butyl
A209 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-n-propyl
A210 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-iso-propyl
A211 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-t-butyl
A212 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-iso-butyl
A213 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-sec-butyl
A214 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-cyclohexyl
A215 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-t-butoxy
A216 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-isopropoxy
A217 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	$-CF_3$
A218 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	$-OCF_3$
A219 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-Cl
A220 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-Br
A221 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-I
A222 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-n-butyl
A223 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-n-propyl
A224 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-iso-propyl
A225 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-t-butyl
A226 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-iso-butyl
A227 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-sec-butyl
A228 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-cyclohexyl
A229 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-t-butoxy
A230 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-isopropoxy
A231 (a, b, c, and d)	-3-(4-chloropyridazinyl)	$-CF_3$

A232 (a, b, c, and d)	-3-(4-chloropyridazinyl)	$-OCF_3$
A233 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-Cl
A234 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-Br
A235 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-I
A236 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-n-butyl
A237 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-n-propyl
A238 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-iso-propyl
A239 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-t-butyl
A240 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-iso-butyl
A241 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-sec-butyl
A242 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-cyclohexyl
A243 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-t-butoxy
A244 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-isopropoxy
A245 (a, b, c, and d)	-3-(4-methylpyridazinyl)	$-CF_3$
A246 (a, b, c, and d)	-3-(4-methylpyridazinyl)	$-OCF_3$
A247 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-Cl
A248 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-Br
A249 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-I
A250 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-n-butyl
A251 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-n-propyl
A252 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-iso-propyl
A253 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-t-butyl
A254 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-iso-butyl
A255 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-sec-butyl
A256 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-cyclohexyl
A257 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-t-butoxy
A258 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-isopropoxy
A259 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	$-CF_3$
A260 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	$-OCF_3$
A261 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-Cl
A262 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-Br
A263 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-I
A264 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-n-butyl
A265 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-n-propyl
A266 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-iso-propyl

A267 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-t-butyl
A268 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-iso-butyl
A269 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-sec-butyl
A270 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-cyclohexyl
A271 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-t-butoxy
A272 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-isopropoxy
A273 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	$-CF_3$
A274 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	$-OCF_3$
A275 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-Cl
A276 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-Br
A277 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-I
A278 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-n-butyl
A279 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-n-propyl
A280 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-iso-propyl
A281 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-t-butyl
A282 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-iso-butyl
A283 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-sec-butyl
A284 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-cyclohexyl
A285 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-t-butoxy
A286 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-isopropoxy
A287 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	$-CF_3$
A288 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	$-OCF_3$
A289 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-Cl
A290 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-Br
A291 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-I
A292 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-n-butyl
A293 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-n-propyl
A294 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-iso-propyl
A295 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-t-butyl
A296 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-iso-butyl
A297 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-sec-butyl
A298 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-cyclohexyl
A299 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-t-butoxy
A300 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-isopropoxy
A301 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	$-CF_3$

A302 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	$-OCF_3$
A303 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-Cl
A304 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-Br
A305 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-I
A306 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-n-butyl
A307 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-n-propyl
A308 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-iso-propyl

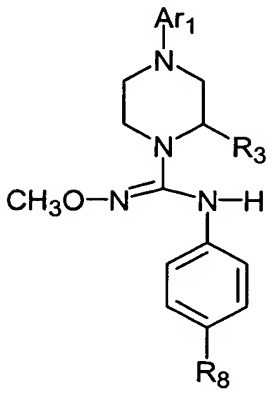
"a" means R_3 is -H.

"b" means R_3 is $-CH_3$ and the Hydroxyiminopiperazine Compound is racemic.

"c" means R_3 is $-CH_3$ and the carbon atom to which R_3 is attached is in the (R) configuration.

"d" means R_3 is $-CH_3$ and the carbon atom to which R_3 is attached is in the (S) configuration.

Table II



and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar_1	R_8
B1 (a, b, c, and d)	-2-(3-chloropyridyl)	-t-butyl
B2 (a, b, c, and d)	-2-(3-chloropyridyl)	-iso-butyl
B3 (a, b, c, and d)	-2-(3-chloropyridyl)	-sec-butyl
B4 (a, b, c, and d)	-2-(3-chloropyridyl)	-cyclohexyl
B5 (a, b, c, and d)	-2-(3-chloropyridyl)	-t-butoxy
B6 (a, b, c, and d)	-2-(3-chloropyridyl)	-isopropoxy
B7 (a, b, c, and d)	-2-(3-chloropyridyl)	$-CF_3$
B8 (a, b, c, and d)	-2-(3-chloropyridyl)	$-OCF_3$
B9 (a, b, c, and d)	-2-(3-chloropyridyl)	-Cl
B10 (a, b, c, and d)	-2-(3-chloropyridyl)	-Br
B11 (a, b, c, and d)	-2-(3-chloropyridyl)	-I
B12 (a, b, c, and d)	-2-(3-chloropyridyl)	-n-butyl
B13 (a, b, c, and d)	-2-(3-chloropyridyl)	-n-propyl
B14 (a, b, c, and d)	-2-(3-chloropyridyl)	-iso-propyl
B15 (a, b, c, and d)	-2-(3-fluoropyridyl)	-t-butyl
B16 (a, b, c, and d)	-2-(3-fluoropyridyl)	-iso-butyl
B17 (a, b, c, and d)	-2-(3-fluoropyridyl)	-sec-butyl
B18 (a, b, c, and d)	-2-(3-fluoropyridyl)	-cyclohexyl
B19 (a, b, c, and d)	-2-(3-fluoropyridyl)	-t-butoxy
B20 (a, b, c, and d)	-2-(3-fluoropyridyl)	-isopropoxy
B21 (a, b, c, and d)	-2-(3-fluoropyridyl)	$-CF_3$
B22 (a, b, c, and d)	-2-(3-fluoropyridyl)	$-OCF_3$

B23 (a, b, c, and d)	-2-(3-fluoropyridyl)	-Cl
B24 (a, b, c, and d)	-2-(3-fluoropyridyl)	-Br
B25 (a, b, c, and d)	-2-(3-fluoropyridyl)	-I
B26 (a, b, c, and d)	-2-(3-fluoropyridyl)	-n-butyl
B27 (a, b, c, and d)	-2-(3-fluoropyridyl)	-n-propyl
B28 (a, b, c, and d)	-2-(3-fluoropyridyl)	-iso-propyl
B29 (a, b, c, and d)	-2-(3-methylpyridyl)	-t-butyl
B30 (a, b, c, and d)	-2-(3-methylpyridyl)	-iso-butyl
B31 (a, b, c, and d)	-2-(3-methylpyridyl)	-sec-butyl
B32 (a, b, c, and d)	-2-(3-methylpyridyl)	-cyclohexyl
B33 (a, b, c, and d)	-2-(3-methylpyridyl)	-t-butoxy
B34 (a, b, c, and d)	-2-(3-methylpyridyl)	-isopropoxy
B35 (a, b, c, and d)	-2-(3-methylpyridyl)	$-CF_3$
B36 (a, b, c, and d)	-2-(3-methylpyridyl)	$-OCF_3$
B37 (a, b, c, and d)	-2-(3-methylpyridyl)	-Cl
B38 (a, b, c, and d)	-2-(3-methylpyridyl)	-Br
B39 (a, b, c, and d)	-2-(3-methylpyridyl)	-I
B40 (a, b, c, and d)	-2-(3-methylpyridyl)	-n-butyl
B41 (a, b, c, and d)	-2-(3-methylpyridyl)	-n-propyl
B42 (a, b, c, and d)	-2-(3-methylpyridyl)	-iso-propyl
B43 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-t-butyl
B44 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-iso-butyl
B45 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-sec-butyl
B46 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-cyclohexyl
B47 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-t-butoxy
B48 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-isopropoxy
B49 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	$-CF_3$
B50 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	$-OCF_3$
B51 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-Cl
B52 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-Br
B53 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-I
B54 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-n-butyl
B55 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-n-propyl
B56 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-iso-propyl
B57 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-t-butyl

B58 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-iso-butyl
B59 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-sec-butyl
B60 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-cyclohexyl
B61 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-t-butoxy
B62 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-isopropoxy
B63 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-CF_3
B64 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-OCF_3
B65 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-Cl
B66 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-Br
B67 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-I
B68 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-n-butyl
B69 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-n-propyl
B70 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-iso-propyl
B71 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-t-butyl
B72 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-iso-butyl
B73 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-sec-butyl
B74 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-cyclohexyl
B75 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-t-butoxy
B76 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-isopropoxy
B77 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-CF_3
B78 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-OCF_3
B79 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-Cl
B80 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-Br
B81 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-I
B82 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-n-butyl
B83 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-n-propyl
B84 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-iso-propyl
B85 (a, b, c, and d)	-2-(3-nitropyridyl)	-t-butyl
B86 (a, b, c, and d)	-2-(3-nitropyridyl)	-iso-butyl
B87 (a, b, c, and d)	-2-(3-nitropyridyl)	-sec-butyl
B88 (a, b, c, and d)	-2-(3-nitropyridyl)	-cyclohexyl
B89 (a, b, c, and d)	-2-(3-nitropyridyl)	-t-butoxy
B90 (a, b, c, and d)	-2-(3-nitropyridyl)	-isopropoxy
B91 (a, b, c, and d)	-2-(3-nitropyridyl)	-CF_3
B92 (a, b, c, and d)	-2-(3-nitropyridyl)	-OCF_3

B93 (a, b, c, and d)	-2-(3-nitropyridyl)	-Cl
B94 (a, b, c, and d)	-2-(3-nitropyridyl)	-Br
B95 (a, b, c, and d)	-2-(3-nitropyridyl)	-I
B96 (a, b, c, and d)	-2-(3-nitropyridyl)	-n-butyl
B97 (a, b, c, and d)	-2-(3-nitropyridyl)	-n-propyl
B98 (a, b, c, and d)	-2-(3-nitropyridyl)	-iso-propyl
B99 (a, b, c, and d)	-2-(3-cyanopyridyl)	-t-butyl
B100 (a, b, c, and d)	-2-(3-cyanopyridyl)	-iso-butyl
B101 (a, b, c, and d)	-2-(3-cyanopyridyl)	-sec-butyl
B102 (a, b, c, and d)	-2-(3-cyanopyridyl)	-cyclohexyl
B103 (a, b, c, and d)	-2-(3-cyanopyridyl)	-t-butoxy
B104 (a, b, c, and d)	-2-(3-cyanopyridyl)	-isopropoxy
B105 (a, b, c, and d)	-2-(3-cyanopyridyl)	$-CF_3$
B106 (a, b, c, and d)	-2-(3-cyanopyridyl)	$-OCF_3$
B107 (a, b, c, and d)	-2-(3-cyanopyridyl)	-Cl
B108 (a, b, c, and d)	-2-(3-cyanopyridyl)	-Br
B109 (a, b, c, and d)	-2-(3-cyanopyridyl)	-I
B110 (a, b, c, and d)	-2-(3-cyanopyridyl)	-n-butyl
B111 (a, b, c, and d)	-2-(3-cyanopyridyl)	-n-propyl
B112 (a, b, c, and d)	-2-(3-cyanopyridyl)	-isopropyl
B113 (a, b, c, and d)	-2-(3-bromopyridyl)	-t-butyl
B114 (a, b, c, and d)	-2-(3-bromopyridyl)	-iso-butyl
B115 (a, b, c, and d)	-2-(3-bromopyridyl)	-sec-butyl
B116 (a, b, c, and d)	-2-(3-bromopyridyl)	-cyclohexyl
B117 (a, b, c, and d)	-2-(3-bromopyridyl)	-t-butoxy
B118 (a, b, c, and d)	-2-(3-bromopyridyl)	-isopropoxy
B119 (a, b, c, and d)	-2-(3-bromopyridyl)	$-CF_3$
B120 (a, b, c, and d)	-2-(3-bromopyridyl)	$-OCF_3$
B121 (a, b, c, and d)	-2-(3-bromopyridyl)	-Cl
B122 (a, b, c, and d)	-2-(3-bromopyridyl)	-Br
B123 (a, b, c, and d)	-2-(3-bromopyridyl)	-I
B124 (a, b, c, and d)	-2-(3-bromopyridyl)	-n-butyl
B125 (a, b, c, and d)	-2-(3-bromopyridyl)	-n-propyl
B126 (a, b, c, and d)	-2-(3-bromopyridyl)	-iso-propyl
B127 (a, b, c, and d)	-2-(3-iodopyridyl)	-t-butyl

B128 (a, b, c, and d)	-2-(3-iodopyridyl)	-iso-butyl
B129 (a, b, c, and d)	-2-(3-iodopyridyl)	-sec-butyl
B130 (a, b, c, and d)	-2-(3-iodopyridyl)	-cyclohexyl
B131 (a, b, c, and d)	-2-(3-iodopyridyl)	-t-butoxy
B132 (a, b, c, and d)	-2-(3-iodopyridyl)	-isopropoxy
B133 (a, b, c, and d)	-2-(3-iodopyridyl)	$-CF_3$
B134 (a, b, c, and d)	-2-(3-iodopyridyl)	$-OCF_3$
B135 (a, b, c, and d)	-2-(3-iodopyridyl)	-Cl
B136 (a, b, c, and d)	-2-(3-iodopyridyl)	-Br
B137 (a, b, c, and d)	-2-(3-iodopyridyl)	-I
B138 (a, b, c, and d)	-2-(3-iodopyridyl)	-n-butyl
B139 (a, b, c, and d)	-2-(3-iodopyridyl)	-n-propyl
B140 (a, b, c, and d)	-2-(3-iodopyridyl)	-iso-propyl
B141 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-t-butyl
B142 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-iso-butyl
B143 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-sec-butyl
B144 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-cyclohexyl
B145 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-t-butoxy
B146 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-isopropoxy
B147 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	$-CF_3$
B148 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	$-OCF_3$
B149 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-Cl
B150 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-Br
B151 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-I
B152 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-n-butyl
B153 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-n-propyl
B154 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-iso-propyl
B155 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-t-butyl
B156 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-iso-butyl
B157 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-sec-butyl
B158 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-cyclohexyl
B159 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-t-butoxy
B160 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-isopropoxy
B161 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	$-CF_3$
B162 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	$-OCF_3$

B163 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-Cl
B164 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-Br
B165 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-I
B166 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-n-butyl
B167 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-n-propyl
B168 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-iso-propyl
B169 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-t-butyl
B170 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-iso-butyl
B171 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-sec-butyl
B172 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-cyclohexyl
B173 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-t-butoxy
B174 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-isopropoxy
B175 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	$-CF_3$
B176 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	$-OCF_3$
B177 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-Cl
B178 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-Br
B179 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-I
B180 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-n-butyl
B181 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-n-propyl
B182 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-iso-propyl
B183 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-t-butyl
B184 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-iso-butyl
B185 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-sec-butyl
B186 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-cyclohexyl
B187 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-t-butoxy
B188 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-isopropoxy
B189 (a, b, c, and d)	-2-(3-chloropyrazinyl)	$-CF_3$
B190 (a, b, c, and d)	-2-(3-chloropyrazinyl)	$-OCF_3$
B191 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-Cl
B192 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-Br
B193 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-I
B194 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-n-butyl
B195 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-n-propyl
B196 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-iso-propyl
B197 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-t-butyl

B198 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-iso-butyl
B199 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-sec-butyl
B200 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-cyclohexyl
B201 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-t-butoxy
B202 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-isopropoxy
B203 (a, b, c, and d)	-2-(3-methylpyrazinyl)	$-CF_3$
B204 (a, b, c, and d)	-2-(3-methylpyrazinyl)	$-OCF_3$
B205 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-Cl
B206 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-Br
B207 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-I
B208 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-n-butyl
B209 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-n-propyl
B210 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-iso-propyl
B211 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-t-butyl
B212 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-iso-butyl
B213 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-sec-butyl
B214 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-cyclohexyl
B215 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-t-butoxy
B216 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-isopropoxy
B217 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	$-CF_3$
B218 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	$-OCF_3$
B219 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-Cl
B220 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-Br
B221 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-I
B222 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-n-butyl
B223 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-n-propyl
B224 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-iso-propyl
B225 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-t-butyl
B226 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-iso-butyl
B227 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-sec-butyl
B228 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-cyclohexyl
B229 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-t-butoxy
B230 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-isopropoxy
B231 (a, b, c, and d)	-3-(4-chloropyridazinyl)	$-CF_3$
B232 (a, b, c, and d)	-3-(4-chloropyridazinyl)	$-OCF_3$

B233 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-Cl
B234 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-Br
B235 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-I
B236 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-n-butyl
B237 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-n-propyl
B238 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-iso-propyl
B239 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-t-butyl
B240 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-iso-butyl
B241 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-sec-butyl
B242 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-cyclohexyl
B243 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-t-butoxy
B244 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-isopropoxy
B245 (a, b, c, and d)	-3-(4-methylpyridazinyl)	$-CF_3$
B246 (a, b, c, and d)	-3-(4-methylpyridazinyl)	$-OCF_3$
B247 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-Cl
B248 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-Br
B249 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-I
B250 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-n-butyl
B251 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-n-propyl
B252 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-iso-propyl
B253 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-t-butyl
B254 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-iso-butyl
B255 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-sec-butyl
B256 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-cyclohexyl
B257 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-t-butoxy
B258 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-isopropoxy
B259 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	$-CF_3$
B260 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	$-OCF_3$
B261 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-Cl
B262 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-Br
B263 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-I
B264 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-n-butyl
B265 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-n-propyl
B266 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-iso-propyl
B267 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-t-butyl

B268 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-iso-butyl
B269 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-sec-butyl
B270 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-cyclohexyl
B271 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-t-butoxy
B272 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-isopropoxy
B273 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	$-CF_3$
B274 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	$-OCF_3$
B275 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-Cl
B276 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-Br
B277 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-I
B278 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-n-butyl
B279 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-n-propyl
B280 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-iso-propyl
B281 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-t-butyl
B282 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-iso-butyl
B283 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-sec-butyl
B284 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-cyclohexyl
B285 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-t-butoxy
B286 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-isopropoxy
B287 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	$-CF_3$
B288 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	$-OCF_3$
B289 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-Cl
B290 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-Br
B291 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-I
B292 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-n-butyl
B293 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-n-propyl
B294 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-iso-propyl
B295 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-t-butyl
B296 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-iso-butyl
B297 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-sec-butyl
B298 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-cyclohexyl
B299 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-t-butoxy
B300 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-isopropoxy
B301 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	$-CF_3$
B302 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	$-OCF_3$

B303 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-Cl
B304 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-Br
B305 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-I
B306 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-n-butyl
B307 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-n-propyl
B308 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-iso-propyl

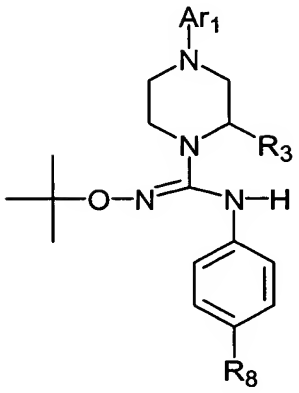
"a" means R_3 is -H.

"b" means R_3 is $-CH_3$ and the Hydroxyiminopiperazine Compound is racemic.

"c" means R_3 is $-CH_3$ and the carbon atom to which R_3 is attached is in the (R) configuration.

"d" means R_3 is $-CH_3$ and the carbon atom to which R_3 is attached is in the (S) configuration.

Table III



and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar_1	R_8
C1 (a, b, c, and d)	-2-(3-chloropyridyl)	-t-butyl
C2 (a, b, c, and d)	-2-(3-chloropyridyl)	-iso-butyl
C3 (a, b, c, and d)	-2-(3-chloropyridyl)	-sec-butyl
C4 (a, b, c, and d)	-2-(3-chloropyridyl)	-cyclohexyl
C5 (a, b, c, and d)	-2-(3-chloropyridyl)	-t-butoxy
C6 (a, b, c, and d)	-2-(3-chloropyridyl)	-isopropoxy
C7 (a, b, c, and d)	-2-(3-chloropyridyl)	$-CF_3$
C8 (a, b, c, and d)	-2-(3-chloropyridyl)	$-OCF_3$
C9 (a, b, c, and d)	-2-(3-chloropyridyl)	-Cl
C10 (a, b, c, and d)	-2-(3-chloropyridyl)	-Br
C11 (a, b, c, and d)	-2-(3-chloropyridyl)	-I
C12 (a, b, c, and d)	-2-(3-chloropyridyl)	-n-butyl
C13 (a, b, c, and d)	-2-(3-chloropyridyl)	-n-propyl
C14 (a, b, c, and d)	-2-(3-chloropyridyl)	-iso-propyl
C15 (a, b, c, and d)	-2-(3-fluoropyridyl)	-t-butyl
C16 (a, b, c, and d)	-2-(3-fluoropyridyl)	-iso-butyl
C17 (a, b, c, and d)	-2-(3-fluoropyridyl)	-sec-butyl
C18 (a, b, c, and d)	-2-(3-fluoropyridyl)	-cyclohexyl
C19 (a, b, c, and d)	-2-(3-fluoropyridyl)	-t-butoxy
C20 (a, b, c, and d)	-2-(3-fluoropyridyl)	-isopropoxy
C21 (a, b, c, and d)	-2-(3-fluoropyridyl)	$-CF_3$
C22 (a, b, c, and d)	-2-(3-fluoropyridyl)	$-OCF_3$

C23 (a, b, c, and d)	-2-(3-fluoropyridyl)	-Cl
C24 (a, b, c, and d)	-2-(3-fluoropyridyl)	-Br
C25 (a, b, c, and d)	-2-(3-fluoropyridyl)	-I
C26 (a, b, c, and d)	-2-(3-fluoropyridyl)	-n-butyl
C27 (a, b, c, and d)	-2-(3-fluoropyridyl)	-n-propyl
C28 (a, b, c, and d)	-2-(3-fluoropyridyl)	-iso-propyl
C29 (a, b, c, and d)	-2-(3-methylpyridyl)	-t-butyl
C30 (a, b, c, and d)	-2-(3-methylpyridyl)	-iso-butyl
C31 (a, b, c, and d)	-2-(3-methylpyridyl)	-sec-butyl
C32 (a, b, c, and d)	-2-(3-methylpyridyl)	-cyclohexyl
C33 (a, b, c, and d)	-2-(3-methylpyridyl)	-t-butoxy
C34 (a, b, c, and d)	-2-(3-methylpyridyl)	-isopropoxy
C35 (a, b, c, and d)	-2-(3-methylpyridyl)	$-CF_3$
C36 (a, b, c, and d)	-2-(3-methylpyridyl)	$-OCF_3$
C37 (a, b, c, and d)	-2-(3-methylpyridyl)	-Cl
C38 (a, b, c, and d)	-2-(3-methylpyridyl)	-Br
C39 (a, b, c, and d)	-2-(3-methylpyridyl)	-I
C40 (a, b, c, and d)	-2-(3-methylpyridyl)	-n-butyl
C41 (a, b, c, and d)	-2-(3-methylpyridyl)	-n-propyl
C42 (a, b, c, and d)	-2-(3-methylpyridyl)	-iso-propyl
C43 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-t-butyl
C44 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-iso-butyl
C45 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-sec-butyl
C46 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-cyclohexyl
C47 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-t-butoxy
C48 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-isopropoxy
C49 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	$-CF_3$
C50 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	$-OCF_3$
C51 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-Cl
C52 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-Br
C53 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-I
C54 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-n-butyl
C55 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-n-propyl
C56 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-iso-propyl
C57 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-t-butyl

C58 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-iso-butyl
C59 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-sec-butyl
C60 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-cyclohexyl
C61 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-t-butoxy
C62 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-isopropoxy
C63 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-CF_3
C64 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-OCF_3
C65 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-Cl
C66 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-Br
C67 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-I
C68 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-n-butyl
C69 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-n-propyl
C70 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-iso-propyl
C71 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-t-butyl
C72 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-iso-butyl
C73 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-sec-butyl
C74 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-cyclohexyl
C75 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-t-butoxy
C76 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-isopropoxy
C77 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-CF_3
C78 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-OCF_3
C79 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-Cl
C80 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-Br
C81 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-I
C82 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-n-butyl
C83 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-n-propyl
C84 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-iso-propyl
C85 (a, b, c, and d)	-2-(3-nitropyridyl)	-t-butyl
C86 (a, b, c, and d)	-2-(3-nitropyridyl)	-iso-butyl
C87 (a, b, c, and d)	-2-(3-nitropyridyl)	-sec-butyl
C88 (a, b, c, and d)	-2-(3-nitropyridyl)	-cyclohexyl
C89 (a, b, c, and d)	-2-(3-nitropyridyl)	-t-butoxy
C90 (a, b, c, and d)	-2-(3-nitropyridyl)	-isopropoxy
C91 (a, b, c, and d)	-2-(3-nitropyridyl)	-CF_3
C92 (a, b, c, and d)	-2-(3-nitropyridyl)	-OCF_3

C93 (a, b, c, and d)	-2-(3-nitropyridyl)	-Cl
C94 (a, b, c, and d)	-2-(3-nitropyridyl)	-Br
C95 (a, b, c, and d)	-2-(3-nitropyridyl)	-I
C96 (a, b, c, and d)	-2-(3-nitropyridyl)	-n-butyl
C97 (a, b, c, and d)	-2-(3-nitropyridyl)	-n-propyl
C98 (a, b, c, and d)	-2-(3-nitropyridyl)	-iso-propyl
C99 (a, b, c, and d)	-2-(3-cyanopyridyl)	-t-butyl
C100 (a, b, c, and d)	-2-(3-cyanopyridyl)	-iso-butyl
C101 (a, b, c, and d)	-2-(3-cyanopyridyl)	-sec-butyl
C102 (a, b, c, and d)	-2-(3-cyanopyridyl)	-cyclohexyl
C103 (a, b, c, and d)	-2-(3-cyanopyridyl)	-t-butoxy
C104 (a, b, c, and d)	-2-(3-cyanopyridyl)	-isopropoxy
C105 (a, b, c, and d)	-2-(3-cyanopyridyl)	$-CF_3$
C106 (a, b, c, and d)	-2-(3-cyanopyridyl)	$-OCF_3$
C107 (a, b, c, and d)	-2-(3-cyanopyridyl)	-Cl
C108 (a, b, c, and d)	-2-(3-cyanopyridyl)	-Br
C109 (a, b, c, and d)	-2-(3-cyanopyridyl)	-I
C110 (a, b, c, and d)	-2-(3-cyanopyridyl)	-n-butyl
C111 (a, b, c, and d)	-2-(3-cyanopyridyl)	-n-propyl
C112 (a, b, c, and d)	-2-(3-cyanopyridyl)	-isopropyl
C113 (a, b, c, and d)	-2-(3-bromopyridyl)	-t-butyl
C114 (a, b, c, and d)	-2-(3-bromopyridyl)	-iso-butyl
C115 (a, b, c, and d)	-2-(3-bromopyridyl)	-sec-butyl
C116 (a, b, c, and d)	-2-(3-bromopyridyl)	-cyclohexyl
C117 (a, b, c, and d)	-2-(3-bromopyridyl)	-t-butoxy
C118 (a, b, c, and d)	-2-(3-bromopyridyl)	-isopropoxy
C119 (a, b, c, and d)	-2-(3-bromopyridyl)	$-CF_3$
C120 (a, b, c, and d)	-2-(3-bromopyridyl)	$-OCF_3$
C121 (a, b, c, and d)	-2-(3-bromopyridyl)	-Cl
C122 (a, b, c, and d)	-2-(3-bromopyridyl)	-Br
C123 (a, b, c, and d)	-2-(3-bromopyridyl)	-I
C124 (a, b, c, and d)	-2-(3-bromopyridyl)	-n-butyl
C125 (a, b, c, and d)	-2-(3-bromopyridyl)	-n-propyl
C126 (a, b, c, and d)	-2-(3-bromopyridyl)	-iso-propyl
C127 (a, b, c, and d)	-2-(3-iodopyridyl)	-t-butyl

C128 (a, b, c, and d)	-2-(3-iodopyridyl)	-iso-butyl
C129 (a, b, c, and d)	-2-(3-iodopyridyl)	-sec-butyl
C130 (a, b, c, and d)	-2-(3-iodopyridyl)	-cyclohexyl
C131 (a, b, c, and d)	-2-(3-iodopyridyl)	-t-butoxy
C132 (a, b, c, and d)	-2-(3-iodopyridyl)	-isopropoxy
C133 (a, b, c, and d)	-2-(3-iodopyridyl)	$-CF_3$
C134 (a, b, c, and d)	-2-(3-iodopyridyl)	$-OCF_3$
C135 (a, b, c, and d)	-2-(3-iodopyridyl)	-Cl
C136 (a, b, c, and d)	-2-(3-iodopyridyl)	-Br
C137 (a, b, c, and d)	-2-(3-iodopyridyl)	-I
C138 (a, b, c, and d)	-2-(3-iodopyridyl)	-n-butyl
C139 (a, b, c, and d)	-2-(3-iodopyridyl)	-n-propyl
C140 (a, b, c, and d)	-2-(3-iodopyridyl)	-iso-propyl
C141 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-t-butyl
C142 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-iso-butyl
C143 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-sec-butyl
C144 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-cyclohexyl
C145 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-t-butoxy
C146 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-isopropoxy
C147 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	$-CF_3$
C148 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	$-OCF_3$
C149 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-Cl
C150 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-Br
C151 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-I
C152 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-n-butyl
C153 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-n-propyl
C154 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-iso-propyl
C155 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-t-butyl
C156 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-iso-butyl
C157 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-sec-butyl
C158 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-cyclohexyl
C159 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-t-butoxy
C160 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-isopropoxy
C161 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	$-CF_3$
C162 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	$-OCF_3$

C163 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-Cl
C164 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-Br
C165 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-I
C166 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-n-butyl
C167 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-n-propyl
C168 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-iso-propyl
C169 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-t-butyl
C170 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-iso-butyl
C171 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-sec-butyl
C172 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-cyclohexyl
C173 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-t-butoxy
C174 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-isopropoxy
C175 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	$-CF_3$
C176 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	$-OCF_3$
C177 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-Cl
C178 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-Br
C179 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-I
C180 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-n-butyl
C181 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-n-propyl
C182 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-iso-propyl
C183 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-t-butyl
C184 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-iso-butyl
C185 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-sec-butyl
C186 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-cyclohexyl
C187 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-t-butoxy
C188 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-isopropoxy
C189 (a, b, c, and d)	-2-(3-chloropyrazinyl)	$-CF_3$
C190 (a, b, c, and d)	-2-(3-chloropyrazinyl)	$-OCF_3$
C191 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-Cl
C192 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-Br
C193 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-I
C194 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-n-butyl
C195 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-n-propyl
C196 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-iso-propyl
C197 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-t-butyl

C198 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-iso-butyl
C199 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-sec-butyl
C200 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-cyclohexyl
C201 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-t-butoxy
C202 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-isopropoxy
C203 (a, b, c, and d)	-2-(3-methylpyrazinyl)	$-CF_3$
C204 (a, b, c, and d)	-2-(3-methylpyrazinyl)	$-OCF_3$
C205 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-Cl
C206 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-Br
C207 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-I
C208 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-n-butyl
C209 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-n-propyl
C210 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-iso-propyl
C211 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-t-butyl
C212 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-iso-butyl
C213 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-sec-butyl
C214 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-cyclohexyl
C215 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-t-butoxy
C216 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-isopropoxy
C217 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	$-CF_3$
C218 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	$-OCF_3$
C219 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-Cl
C220 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-Br
C221 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-I
C222 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-n-butyl
C223 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-n-propyl
C224 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-iso-propyl
C225 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-t-butyl
C226 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-iso-butyl
C227 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-sec-butyl
C228 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-cyclohexyl
C229 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-t-butoxy
C230 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-isopropoxy
C231 (a, b, c, and d)	-3-(4-chloropyridazinyl)	$-CF_3$
C232 (a, b, c, and d)	-3-(4-chloropyridazinyl)	$-OCF_3$

C233 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-Cl
C234 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-Br
C235 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-I
C236 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-n-butyl
C237 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-n-propyl
C238 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-iso-propyl
C239 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-t-butyl
C240 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-iso-butyl
C241 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-sec-butyl
C242 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-cyclohexyl
C243 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-t-butoxy
C244 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-isopropoxy
C245 (a, b, c, and d)	-3-(4-methylpyridazinyl)	$-CF_3$
C246 (a, b, c, and d)	-3-(4-methylpyridazinyl)	$-OCF_3$
C247 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-Cl
C248 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-Br
C249 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-I
C250 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-n-butyl
C251 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-n-propyl
C252 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-iso-propyl
C253 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-t-butyl
C254 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-iso-butyl
C255 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-sec-butyl
C256 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-cyclohexyl
C257 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-t-butoxy
C258 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-isopropoxy
C259 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	$-CF_3$
C260 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	$-OCF_3$
C261 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-Cl
C262 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-Br
C263 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-I
C264 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-n-butyl
C265 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-n-propyl
C266 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-iso-propyl
C267 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-t-butyl

C268 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-iso-butyl
C269 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-sec-butyl
C270 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-cyclohexyl
C271 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-t-butoxy
C272 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-isopropoxy
C273 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	$-CF_3$
C274 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	$-OCF_3$
C275 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-Cl
C276 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-Br
C277 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-I
C278 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-n-butyl
C279 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-n-propyl
C280 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-iso-propyl
C281 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-t-butyl
C282 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-iso-butyl
C283 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-sec-butyl
C284 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-cyclohexyl
C285 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-t-butoxy
C286 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-isopropoxy
C287 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	$-CF_3$
C288 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	$-OCF_3$
C289 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-Cl
C290 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-Br
C291 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-I
C292 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-n-butyl
C293 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-n-propyl
C294 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-iso-propyl
C295 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-t-butyl
C296 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-iso-butyl
C297 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-sec-butyl
C298 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-cyclohexyl
C299 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-t-butoxy
C300 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-isopropoxy
C301 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	$-CF_3$
C302 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	$-OCF_3$

C303 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-Cl
C304 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-Br
C305 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-I
C306 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-n-butyl
C307 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-n-propyl
C308 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-iso-propyl

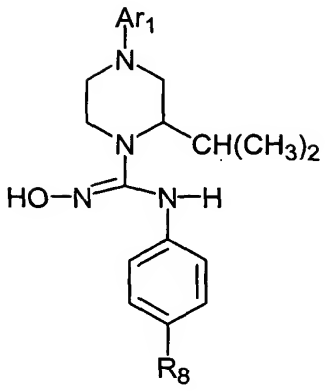
"a" means R_3 is -H.

"b" means R_3 is $-CH_3$ and the Hydroxyiminopiperazine Compound is racemic.

"c" means R_3 is $-CH_3$ and the carbon atom to which R_3 is attached is in the (R) configuration.

"d" means R_3 is $-CH_3$ and the carbon atom to which R_3 is attached is in the (S) configuration.

Table IV



and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar_1	R_8
D1 (a, b, and c)	-2-(3-chloropyridyl)	-t-butyl
D2 (a, b, and c)	-2-(3-chloropyridyl)	-iso-butyl
D3 (a, b, and c)	-2-(3-chloropyridyl)	-sec-butyl
D4 (a, b, and c)	-2-(3-chloropyridyl)	-cyclohexyl
D5 (a, b, and c)	-2-(3-chloropyridyl)	-t-butoxy
D6 (a, b, and c)	-2-(3-chloropyridyl)	-isopropoxy
D7 (a, b, and c)	-2-(3-chloropyridyl)	$-CF_3$
D8 (a, b, and c)	-2-(3-chloropyridyl)	$-OCF_3$
D9 (a, b, and c)	-2-(3-chloropyridyl)	-Cl
D10 (a, b, and c)	-2-(3-chloropyridyl)	-Br
D11 (a, b, and c)	-2-(3-chloropyridyl)	-I
D12 (a, b, and c)	-2-(3-chloropyridyl)	-n-butyl
D13 (a, b, and c)	-2-(3-chloropyridyl)	-n-propyl
D14 (a, b, and c)	-2-(3-chloropyridyl)	-iso-propyl
D15 (a, b, and c)	-2-(3-fluoropyridyl)	-t-butyl
D16 (a, b, and c)	-2-(3-fluoropyridyl)	-iso-butyl
D17 (a, b, and c)	-2-(3-fluoropyridyl)	-sec-butyl
D18 (a, b, and c)	-2-(3-fluoropyridyl)	-cyclohexyl
D19 (a, b, and c)	-2-(3-fluoropyridyl)	-t-butoxy
D20 (a, b, and c)	-2-(3-fluoropyridyl)	-isopropoxy
D21 (a, b, and c)	-2-(3-fluoropyridyl)	$-CF_3$
D22 (a, b, and c)	-2-(3-fluoropyridyl)	$-OCF_3$

D23 (a, b, and c)	-2-(3-fluoropyridyl)	-Cl
D24 (a, b, and c)	-2-(3-fluoropyridyl)	-Br
D25 (a, b, and c)	-2-(3-fluoropyridyl)	-I
D26 (a, b, and c)	-2-(3-fluoropyridyl)	-n-butyl
D27 (a, b, and c)	-2-(3-fluoropyridyl)	-n-propyl
D28 (a, b, and c)	-2-(3-fluoropyridyl)	-iso-propyl
D29 (a, b, and c)	-2-(3-methylpyridyl)	-t-butyl
D30 (a, b, and c)	-2-(3-methylpyridyl)	-iso-butyl
D31 (a, b, and c)	-2-(3-methylpyridyl)	-sec-butyl
D32 (a, b, and c)	-2-(3-methylpyridyl)	-cyclohexyl
D33 (a, b, and c)	-2-(3-methylpyridyl)	-t-butoxy
D34 (a, b, and c)	-2-(3-methylpyridyl)	-isopropoxy
D35 (a, b, and c)	-2-(3-methylpyridyl)	$-CF_3$
D36 (a, b, and c)	-2-(3-methylpyridyl)	$-OCF_3$
D37 (a, b, and c)	-2-(3-methylpyridyl)	-Cl
D38 (a, b, and c)	-2-(3-methylpyridyl)	-Br
D39 (a, b, and c)	-2-(3-methylpyridyl)	-I
D40 (a, b, and c)	-2-(3-methylpyridyl)	-n-butyl
D41 (a, b, and c)	-2-(3-methylpyridyl)	-n-propyl
D42 (a, b, and c)	-2-(3-methylpyridyl)	-iso-propyl
D43 (a, b, and c)	-2-(3-CF_3-pyridyl)	-t-butyl
D44 (a, b, and c)	-2-(3-CF_3-pyridyl)	-iso-butyl
D45 (a, b, and c)	-2-(3-CF_3-pyridyl)	-sec-butyl
D46 (a, b, and c)	-2-(3-CF_3-pyridyl)	-cyclohexyl
D47 (a, b, and c)	-2-(3-CF_3-pyridyl)	-t-butoxy
D48 (a, b, and c)	-2-(3-CF_3-pyridyl)	-isopropoxy
D49 (a, b, and c)	-2-(3-CF_3-pyridyl)	$-CF_3$
D50 (a, b, and c)	-2-(3-CF_3-pyridyl)	$-OCF_3$
D51 (a, b, and c)	-2-(3-CF_3-pyridyl)	-Cl
D52 (a, b, and c)	-2-(3-CF_3-pyridyl)	-Br
D53 (a, b, and c)	-2-(3-CF_3-pyridyl)	-I
D54 (a, b, and c)	-2-(3-CF_3-pyridyl)	-n-butyl
D55 (a, b, and c)	-2-(3-CF_3-pyridyl)	-n-propyl
D56 (a, b, and c)	-2-(3-CF_3-pyridyl)	-iso-propyl
D57 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-t-butyl

D58 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-iso-butyl
D59 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-sec-butyl
D60 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-cyclohexyl
D61 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-t-butoxy
D62 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-isopropoxy
D63 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-CF_3
D64 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-OCF_3
D65 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-Cl
D66 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-Br
D67 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-I
D68 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-n-butyl
D69 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-n-propyl
D70 (a, b, and c)	-2-(3-CHF_2-pyridyl)	-iso-propyl
D71 (a, b, and c)	-2-(3-hydroxypyridyl)	-t-butyl
D72 (a, b, and c)	-2-(3-hydroxypyridyl)	-iso-butyl
D73 (a, b, and c)	-2-(3-hydroxypyridyl)	-sec-butyl
D74 (a, b, and c)	-2-(3-hydroxypyridyl)	-cyclohexyl
D75 (a, b, and c)	-2-(3-hydroxypyridyl)	-t-butoxy
D76 (a, b, and c)	-2-(3-hydroxypyridyl)	-isopropoxy
D77 (a, b, and c)	-2-(3-hydroxypyridyl)	-CF_3
D78 (a, b, and c)	-2-(3-hydroxypyridyl)	-OCF_3
D79 (a, b, and c)	-2-(3-hydroxypyridyl)	-Cl
D80 (a, b, and c)	-2-(3-hydroxypyridyl)	-Br
D81 (a, b, and c)	-2-(3-hydroxypyridyl)	-I
D82 (a, b, and c)	-2-(3-hydroxypyridyl)	-n-butyl
D83 (a, b, and c)	-2-(3-hydroxypyridyl)	-n-propyl
D84 (a, b, and c)	-2-(3-hydroxypyridyl)	-iso-propyl
D85 (a, b, and c)	-2-(3-nitropyridyl)	-t-butyl
D86 (a, b, and c)	-2-(3-nitropyridyl)	-iso-butyl
D87 (a, b, and c)	-2-(3-nitropyridyl)	-sec-butyl
D88 (a, b, and c)	-2-(3-nitropyridyl)	-cyclohexyl
D89 (a, b, and c)	-2-(3-nitropyridyl)	-t-butoxy
D90 (a, b, and c)	-2-(3-nitropyridyl)	-isopropoxy
D91 (a, b, and c)	-2-(3-nitropyridyl)	-CF_3
D92 (a, b, and c)	-2-(3-nitropyridyl)	-OCF_3

D93 (a, b, and c)	-2-(3-nitropyridyl)	-Cl
D94 (a, b, and c)	-2-(3-nitropyridyl)	-Br
D95 (a, b, and c)	-2-(3-nitropyridyl)	-I
D96 (a, b, and c)	-2-(3-nitropyridyl)	-n-butyl
D97 (a, b, and c)	-2-(3-nitropyridyl)	-n-propyl
D98 (a, b, and c)	-2-(3-nitropyridyl)	-iso-propyl
D99 (a, b, and c)	-2-(3-cyanopyridyl)	-t-butyl
D100 (a, b, and c)	-2-(3-cyanopyridyl)	-iso-butyl
D101 (a, b, and c)	-2-(3-cyanopyridyl)	-sec-butyl
D102 (a, b, and c)	-2-(3-cyanopyridyl)	-cyclohexyl
D103 (a, b, and c)	-2-(3-cyanopyridyl)	-t-butoxy
D104 (a, b, and c)	-2-(3-cyanopyridyl)	-isopropoxy
D105 (a, b, and c)	-2-(3-cyanopyridyl)	$-CF_3$
D106 (a, b, and c)	-2-(3-cyanopyridyl)	$-OCF_3$
D107 (a, b, and c)	-2-(3-cyanopyridyl)	-Cl
D108 (a, b, and c)	-2-(3-cyanopyridyl)	-Br
D109 (a, b, and c)	-2-(3-cyanopyridyl)	-I
D110 (a, b, and c)	-2-(3-cyanopyridyl)	-n-butyl
D111 (a, b, and c)	-2-(3-cyanopyridyl)	-n-propyl
D112 (a, b, and c)	-2-(3-cyanopyridyl)	-isopropyl
D113 (a, b, and c)	-2-(3-bromopyridyl)	-t-butyl
D114 (a, b, and c)	-2-(3-bromopyridyl)	-iso-butyl
D115 (a, b, and c)	-2-(3-bromopyridyl)	-sec-butyl
D116 (a, b, and c)	-2-(3-bromopyridyl)	-cyclohexyl
D117 (a, b, and c)	-2-(3-bromopyridyl)	-t-butoxy
D118 (a, b, and c)	-2-(3-bromopyridyl)	-isopropoxy
D119 (a, b, and c)	-2-(3-bromopyridyl)	$-CF_3$
D120 (a, b, and c)	-2-(3-bromopyridyl)	$-OCF_3$
D121 (a, b, and c)	-2-(3-bromopyridyl)	-Cl
D122 (a, b, and c)	-2-(3-bromopyridyl)	-Br
D123 (a, b, and c)	-2-(3-bromopyridyl)	-I
D124 (a, b, and c)	-2-(3-bromopyridyl)	-n-butyl
D125 (a, b, and c)	-2-(3-bromopyridyl)	-n-propyl
D126 (a, b, and c)	-2-(3-bromopyridyl)	-iso-propyl
D127 (a, b, and c)	-2-(3-iodopyridyl)	-t-butyl

D128 (a, b, and c)	-2-(3-iodopyridyl)	-iso-butyl
D129 (a, b, and c)	-2-(3-iodopyridyl)	-sec-butyl
D130 (a, b, and c)	-2-(3-iodopyridyl)	-cyclohexyl
D131 (a, b, and c)	-2-(3-iodopyridyl)	-t-butoxy
D132 (a, b, and c)	-2-(3-iodopyridyl)	-isopropoxy
D133 (a, b, and c)	-2-(3-iodopyridyl)	$-CF_3$
D134 (a, b, and c)	-2-(3-iodopyridyl)	$-OCF_3$
D135 (a, b, and c)	-2-(3-iodopyridyl)	-Cl
D136 (a, b, and c)	-2-(3-iodopyridyl)	-Br
D137 (a, b, and c)	-2-(3-iodopyridyl)	-I
D138 (a, b, and c)	-2-(3-iodopyridyl)	-n-butyl
D139 (a, b, and c)	-2-(3-iodopyridyl)	-n-propyl
D140 (a, b, and c)	-2-(3-iodopyridyl)	-iso-propyl
D141 (a, b, and c)	-4-(5-chloropyrimidinyl)	-t-butyl
D142 (a, b, and c)	-4-(5-chloropyrimidinyl)	-iso-butyl
D143 (a, b, and c)	-4-(5-chloropyrimidinyl)	-sec-butyl
D144 (a, b, and c)	-4-(5-chloropyrimidinyl)	-cyclohexyl
D145 (a, b, and c)	-4-(5-chloropyrimidinyl)	-t-butoxy
D146 (a, b, and c)	-4-(5-chloropyrimidinyl)	-isopropoxy
D147 (a, b, and c)	-4-(5-chloropyrimidinyl)	$-CF_3$
D148 (a, b, and c)	-4-(5-chloropyrimidinyl)	$-OCF_3$
D149 (a, b, and c)	-4-(5-chloropyrimidinyl)	-Cl
D150 (a, b, and c)	-4-(5-chloropyrimidinyl)	-Br
D151 (a, b, and c)	-4-(5-chloropyrimidinyl)	-I
D152 (a, b, and c)	-4-(5-chloropyrimidinyl)	-n-butyl
D153 (a, b, and c)	-4-(5-chloropyrimidinyl)	-n-propyl
D154 (a, b, and c)	-4-(5-chloropyrimidinyl)	-iso-propyl
D155 (a, b, and c)	-4-(5-methylpyrimidinyl)	-t-butyl
D156 (a, b, and c)	-4-(5-methylpyrimidinyl)	-iso-butyl
D157 (a, b, and c)	-4-(5-methylpyrimidinyl)	-sec-butyl
D158 (a, b, and c)	-4-(5-methylpyrimidinyl)	-cyclohexyl
D159 (a, b, and c)	-4-(5-methylpyrimidinyl)	-t-butoxy
D160 (a, b, and c)	-4-(5-methylpyrimidinyl)	-isopropoxy
D161 (a, b, and c)	-4-(5-methylpyrimidinyl)	$-CF_3$
D162 (a, b, and c)	-4-(5-methylpyrimidinyl)	$-OCF_3$

D163 (a, b, and c)	-4-(5-methylpyrimidinyl)	-Cl
D164 (a, b, and c)	-4-(5-methylpyrimidinyl)	-Br
D165 (a, b, and c)	-4-(5-methylpyrimidinyl)	-I
D166 (a, b, and c)	-4-(5-methylpyrimidinyl)	-n-butyl
D167 (a, b, and c)	-4-(5-methylpyrimidinyl)	-n-propyl
D168 (a, b, and c)	-4-(5-methylpyrimidinyl)	-iso-propyl
D169 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-t-butyl
D170 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-iso-butyl
D171 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-sec-butyl
D172 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-cyclohexyl
D173 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-t-butoxy
D174 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-isopropoxy
D175 (a, b, and c)	-4-(5-fluoropyrimidinyl)	$-CF_3$
D176 (a, b, and c)	-4-(5-fluoropyrimidinyl)	$-OCF_3$
D177 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-Cl
D178 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-Br
D179 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-I
D180 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-n-butyl
D181 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-n-propyl
D182 (a, b, and c)	-4-(5-fluoropyrimidinyl)	-iso-propyl
D183 (a, b, and c)	-2-(3-chloropyrazinyl)	-t-butyl
D184 (a, b, and c)	-2-(3-chloropyrazinyl)	-iso-butyl
D185 (a, b, and c)	-2-(3-chloropyrazinyl)	-sec-butyl
D186 (a, b, and c)	-2-(3-chloropyrazinyl)	-cyclohexyl
D187 (a, b, and c)	-2-(3-chloropyrazinyl)	-t-butoxy
D188 (a, b, and c)	-2-(3-chloropyrazinyl)	-isopropoxy
D189 (a, b, and c)	-2-(3-chloropyrazinyl)	$-CF_3$
D190 (a, b, and c)	-2-(3-chloropyrazinyl)	$-OCF_3$
D191 (a, b, and c)	-2-(3-chloropyrazinyl)	-Cl
D192 (a, b, and c)	-2-(3-chloropyrazinyl)	-Br
D193 (a, b, and c)	-2-(3-chloropyrazinyl)	-I
D194 (a, b, and c)	-2-(3-chloropyrazinyl)	-n-butyl
D195 (a, b, and c)	-2-(3-chloropyrazinyl)	-n-propyl
D196 (a, b, and c)	-2-(3-chloropyrazinyl)	-iso-propyl
D197 (a, b, and c)	-2-(3-methylpyrazinyl)	-t-butyl

D198 (a, b, and c)	-2-(3-methylpyrazinyl)	-iso-butyl
D199 (a, b, and c)	-2-(3-methylpyrazinyl)	-sec-butyl
D200 (a, b, and c)	-2-(3-methylpyrazinyl)	-cyclohexyl
D201 (a, b, and c)	-2-(3-methylpyrazinyl)	-t-butoxy
D202 (a, b, and c)	-2-(3-methylpyrazinyl)	-isopropoxy
D203 (a, b, and c)	-2-(3-methylpyrazinyl)	$-CF_3$
D204 (a, b, and c)	-2-(3-methylpyrazinyl)	$-OCF_3$
D205 (a, b, and c)	-2-(3-methylpyrazinyl)	-Cl
D206 (a, b, and c)	-2-(3-methylpyrazinyl)	-Br
D207 (a, b, and c)	-2-(3-methylpyrazinyl)	-I
D208 (a, b, and c)	-2-(3-methylpyrazinyl)	-n-butyl
D209 (a, b, and c)	-2-(3-methylpyrazinyl)	-n-propyl
D210 (a, b, and c)	-2-(3-methylpyrazinyl)	-iso-propyl
D211 (a, b, and c)	-2-(3-fluoropyrazinyl)	-t-butyl
D212 (a, b, and c)	-2-(3-fluoropyrazinyl)	-iso-butyl
D213 (a, b, and c)	-2-(3-fluoropyrazinyl)	-sec-butyl
D214 (a, b, and c)	-2-(3-fluoropyrazinyl)	-cyclohexyl
D215 (a, b, and c)	-2-(3-fluoropyrazinyl)	-t-butoxy
D216 (a, b, and c)	-2-(3-fluoropyrazinyl)	-isopropoxy
D217 (a, b, and c)	-2-(3-fluoropyrazinyl)	$-CF_3$
D218 (a, b, and c)	-2-(3-fluoropyrazinyl)	$-OCF_3$
D219 (a, b, and c)	-2-(3-fluoropyrazinyl)	-Cl
D220 (a, b, and c)	-2-(3-fluoropyrazinyl)	-Br
D221 (a, b, and c)	-2-(3-fluoropyrazinyl)	-I
D222 (a, b, and c)	-2-(3-fluoropyrazinyl)	-n-butyl
D223 (a, b, and c)	-2-(3-fluoropyrazinyl)	-n-propyl
D224 (a, b, and c)	-2-(3-fluoropyrazinyl)	-iso-propyl
D225 (a, b, and c)	-3-(4-chloropyridazinyl)	-t-butyl
D226 (a, b, and c)	-3-(4-chloropyridazinyl)	-iso-butyl
D227 (a, b, and c)	-3-(4-chloropyridazinyl)	-sec-butyl
D228 (a, b, and c)	-3-(4-chloropyridazinyl)	-cyclohexyl
D229 (a, b, and c)	-3-(4-chloropyridazinyl)	-t-butoxy
D230 (a, b, and c)	-3-(4-chloropyridazinyl)	-isopropoxy
D231 (a, b, and c)	-3-(4-chloropyridazinyl)	$-CF_3$
D232 (a, b, and c)	-3-(4-chloropyridazinyl)	$-OCF_3$

D233 (a, b, and c)	-3-(4-chloropyridazinyl)	-Cl
D234 (a, b, and c)	-3-(4-chloropyridazinyl)	-Br
D235 (a, b, and c)	-3-(4-chloropyridazinyl)	-I
D236 (a, b, and c)	-3-(4-chloropyridazinyl)	-n-butyl
D237 (a, b, and c)	-3-(4-chloropyridazinyl)	-n-propyl
D238 (a, b, and c)	-3-(4-chloropyridazinyl)	-iso-propyl
D239 (a, b, and c)	-3-(4-methylpyridazinyl)	-t-butyl
D240 (a, b, and c)	-3-(4-methylpyridazinyl)	-iso-butyl
D241 (a, b, and c)	-3-(4-methylpyridazinyl)	-sec-butyl
D242 (a, b, and c)	-3-(4-methylpyridazinyl)	-cyclohexyl
D243 (a, b, and c)	-3-(4-methylpyridazinyl)	-t-butoxy
D244 (a, b, and c)	-3-(4-methylpyridazinyl)	-isopropoxy
D245 (a, b, and c)	-3-(4-methylpyridazinyl)	$-CF_3$
D246 (a, b, and c)	-3-(4-methylpyridazinyl)	$-OCF_3$
D247 (a, b, and c)	-3-(4-methylpyridazinyl)	-Cl
D248 (a, b, and c)	-3-(4-methylpyridazinyl)	-Br
D249 (a, b, and c)	-3-(4-methylpyridazinyl)	-I
D250 (a, b, and c)	-3-(4-methylpyridazinyl)	-n-butyl
D251 (a, b, and c)	-3-(4-methylpyridazinyl)	-n-propyl
D252 (a, b, and c)	-3-(4-methylpyridazinyl)	-iso-propyl
D253 (a, b, and c)	-3-(4-fluoropyridazinyl)	-t-butyl
D254 (a, b, and c)	-3-(4-fluoropyridazinyl)	-iso-butyl
D255 (a, b, and c)	-3-(4-fluoropyridazinyl)	-sec-butyl
D256 (a, b, and c)	-3-(4-fluoropyridazinyl)	-cyclohexyl
D257 (a, b, and c)	-3-(4-fluoropyridazinyl)	-t-butoxy
D258 (a, b, and c)	-3-(4-fluoropyridazinyl)	-isopropoxy
D259 (a, b, and c)	-3-(4-fluoropyridazinyl)	$-CF_3$
D260 (a, b, and c)	-3-(4-fluoropyridazinyl)	$-OCF_3$
D261 (a, b, and c)	-3-(4-fluoropyridazinyl)	-Cl
D262 (a, b, and c)	-3-(4-fluoropyridazinyl)	-Br
D263 (a, b, and c)	-3-(4-fluoropyridazinyl)	-I
D264 (a, b, and c)	-3-(4-fluoropyridazinyl)	-n-butyl
D265 (a, b, and c)	-3-(4-fluoropyridazinyl)	-n-propyl
D266 (a, b, and c)	-3-(4-fluoropyridazinyl)	-iso-propyl
D267 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-t-butyl

D268 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-iso-butyl
D269 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-sec-butyl
D270 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-cyclohexyl
D271 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-t-butoxy
D272 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-isopropoxy
D273 (a, b, and c)	-5-(4-chlorothiadiazolyl)	$-CF_3$
D274 (a, b, and c)	-5-(4-chlorothiadiazolyl)	$-OCF_3$
D275 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-Cl
D276 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-Br
D277 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-I
D278 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-n-butyl
D279 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-n-propyl
D280 (a, b, and c)	-5-(4-chlorothiadiazolyl)	-iso-propyl
D281 (a, b, and c)	-5-(4-methylthiadiazolyl)	-t-butyl
D282 (a, b, and c)	-5-(4-methylthiadiazolyl)	-iso-butyl
D283 (a, b, and c)	-5-(4-methylthiadiazolyl)	-sec-butyl
D284 (a, b, and c)	-5-(4-methylthiadiazolyl)	-cyclohexyl
D285 (a, b, and c)	-5-(4-methylthiadiazolyl)	-t-butoxy
D286 (a, b, and c)	-5-(4-methylthiadiazolyl)	-isopropoxy
D287 (a, b, and c)	-5-(4-methylthiadiazolyl)	$-CF_3$
D288 (a, b, and c)	-5-(4-methylthiadiazolyl)	$-OCF_3$
D289 (a, b, and c)	-5-(4-methylthiadiazolyl)	-Cl
D290 (a, b, and c)	-5-(4-methylthiadiazolyl)	-Br
D291 (a, b, and c)	-5-(4-methylthiadiazolyl)	-I
D292 (a, b, and c)	-5-(4-methylthiadiazolyl)	-n-butyl
D293 (a, b, and c)	-5-(4-methylthiadiazolyl)	-n-propyl
D294 (a, b, and c)	-5-(4-methylthiadiazolyl)	-iso-propyl
D295 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-t-butyl
D296 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-iso-butyl
D297 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-sec-butyl
D298 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-cyclohexyl
D299 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-t-butoxy
D300 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-isopropoxy
D301 (a, b, and c)	-5-(4-fluorothiadiazolyl)	$-CF_3$
D302 (a, b, and c)	-5-(4-fluorothiadiazolyl)	$-OCF_3$

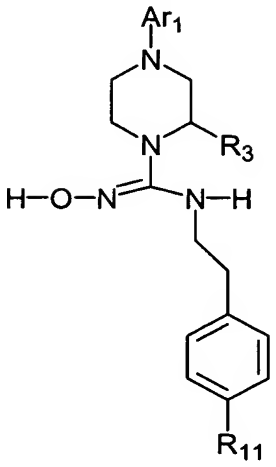
D303 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-Cl
D304 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-Br
D305 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-I
D306 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-n-butyl
D307 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-n-propyl
D308 (a, b, and c)	-5-(4-fluorothiadiazolyl)	-iso-propyl

"a" means that the Hydroxyiminopiperazine Compound is racemic.

"b" means that the carbon atom to which $-CH(CH_3)_2$ is attached is in the (R) configuration.

"c" means that the carbon atom to which $-CH(CH_3)_2$ is attached is in the (S) configuration.

Table V



and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar_1	R_{11}
E1 (a, b, c, and d)	-2-(3-chloropyridyl)	-t-butyl
E2 (a, b, c, and d)	-2-(3-chloropyridyl)	-iso-butyl
E3 (a, b, c, and d)	-2-(3-chloropyridyl)	-sec-butyl
E4 (a, b, c, and d)	-2-(3-chloropyridyl)	-cyclohexyl
E5 (a, b, c, and d)	-2-(3-chloropyridyl)	-t-butoxy
E6 (a, b, c, and d)	-2-(3-chloropyridyl)	-isopropoxy
E7 (a, b, c, and d)	-2-(3-chloropyridyl)	$-CF_3$
E8 (a, b, c, and d)	-2-(3-chloropyridyl)	$-OCF_3$
E9 (a, b, c, and d)	-2-(3-chloropyridyl)	-Cl
E10 (a, b, c, and d)	-2-(3-chloropyridyl)	-Br
E11 (a, b, c, and d)	-2-(3-chloropyridyl)	-I
E12 (a, b, c, and d)	-2-(3-chloropyridyl)	-n-butyl
E13 (a, b, c, and d)	-2-(3-chloropyridyl)	-n-propyl
E14 (a, b, c, and d)	-2-(3-chloropyridyl)	-iso-propyl
E15 (a, b, c, and d)	-2-(3-fluoropyridyl)	-t-butyl
E16 (a, b, c, and d)	-2-(3-fluoropyridyl)	-iso-butyl
E17 (a, b, c, and d)	-2-(3-fluoropyridyl)	-sec-butyl
E18 (a, b, c, and d)	-2-(3-fluoropyridyl)	-cyclohexyl
E19 (a, b, c, and d)	-2-(3-fluoropyridyl)	-t-butoxy
E20 (a, b, c, and d)	-2-(3-fluoropyridyl)	-isopropoxy
E21 (a, b, c, and d)	-2-(3-fluoropyridyl)	$-CF_3$
E22 (a, b, c, and d)	-2-(3-fluoropyridyl)	$-OCF_3$

E23 (a, b, c, and d)	-2-(3-fluoropyridyl)	-Cl
E24 (a, b, c, and d)	-2-(3-fluoropyridyl)	-Br
E25 (a, b, c, and d)	-2-(3-fluoropyridyl)	-I
E26 (a, b, c, and d)	-2-(3-fluoropyridyl)	-n-butyl
E27 (a, b, c, and d)	-2-(3-fluoropyridyl)	-n-propyl
E28 (a, b, c, and d)	-2-(3-fluoropyridyl)	-iso-propyl
E29 (a, b, c, and d)	-2-(3-methylpyridyl)	-t-butyl
E30 (a, b, c, and d)	-2-(3-methylpyridyl)	-iso-butyl
E31 (a, b, c, and d)	-2-(3-methylpyridyl)	-sec-butyl
E32 (a, b, c, and d)	-2-(3-methylpyridyl)	-cyclohexyl
E33 (a, b, c, and d)	-2-(3-methylpyridyl)	-t-butoxy
E34 (a, b, c, and d)	-2-(3-methylpyridyl)	-isopropoxy
E35 (a, b, c, and d)	-2-(3-methylpyridyl)	$-CF_3$
E36 (a, b, c, and d)	-2-(3-methylpyridyl)	$-OCF_3$
E37 (a, b, c, and d)	-2-(3-methylpyridyl)	-Cl
E38 (a, b, c, and d)	-2-(3-methylpyridyl)	-Br
E39 (a, b, c, and d)	-2-(3-methylpyridyl)	-I
E40 (a, b, c, and d)	-2-(3-methylpyridyl)	-n-butyl
E41 (a, b, c, and d)	-2-(3-methylpyridyl)	-n-propyl
E42 (a, b, c, and d)	-2-(3-methylpyridyl)	-iso-propyl
E43 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-t-butyl
E44 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-iso-butyl
E45 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-sec-butyl
E46 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-cyclohexyl
E47 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-t-butoxy
E48 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-isopropoxy
E49 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	$-CF_3$
E50 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	$-OCF_3$
E51 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-Cl
E52 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-Br
E53 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-I
E54 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-n-butyl
E55 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-n-propyl
E56 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-iso-propyl
E57 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-t-butyl

E58 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-iso-butyl
E59 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-sec-butyl
E60 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-cyclohexyl
E61 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-t-butoxy
E62 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-isopropoxy
E63 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-CF_3
E64 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-OCF_3
E65 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-Cl
E66 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-Br
E67 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-I
E68 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-n-butyl
E69 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-n-propyl
E70 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-iso-propyl
E71 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-t-butyl
E72 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-iso-butyl
E73 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-sec-butyl
E74 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-cyclohexyl
E75 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-t-butoxy
E76 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-isopropoxy
E77 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-CF_3
E78 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-OCF_3
E79 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-Cl
E80 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-Br
E81 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-I
E82 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-n-butyl
E83 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-n-propyl
E84 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-iso-propyl
E85 (a, b, c, and d)	-2-(3-nitropyridyl)	-t-butyl
E86 (a, b, c, and d)	-2-(3-nitropyridyl)	-iso-butyl
E87 (a, b, c, and d)	-2-(3-nitropyridyl)	-sec-butyl
E88 (a, b, c, and d)	-2-(3-nitropyridyl)	-cyclohexyl
E89 (a, b, c, and d)	-2-(3-nitropyridyl)	-t-butoxy
E90 (a, b, c, and d)	-2-(3-nitropyridyl)	-isopropoxy
E91 (a, b, c, and d)	-2-(3-nitropyridyl)	-CF_3
E92 (a, b, c, and d)	-2-(3-nitropyridyl)	-OCF_3

E93 (a, b, c, and d)	-2-(3-nitropyridyl)	-Cl
E94 (a, b, c, and d)	-2-(3-nitropyridyl)	-Br
E95 (a, b, c, and d)	-2-(3-nitropyridyl)	-I
E96 (a, b, c, and d)	-2-(3-nitropyridyl)	-n-butyl
E97 (a, b, c, and d)	-2-(3-nitropyridyl)	-n-propyl
E98 (a, b, c, and d)	-2-(3-nitropyridyl)	-iso-propyl
E99 (a, b, c, and d)	-2-(3-cyanopyridyl)	-t-butyl
E100 (a, b, c, and d)	-2-(3-cyanopyridyl)	-iso-butyl
E101 (a, b, c, and d)	-2-(3-cyanopyridyl)	-sec-butyl
E102 (a, b, c, and d)	-2-(3-cyanopyridyl)	-cyclohexyl
E103 (a, b, c, and d)	-2-(3-cyanopyridyl)	-t-butoxy
E104 (a, b, c, and d)	-2-(3-cyanopyridyl)	-isopropoxy
E105 (a, b, c, and d)	-2-(3-cyanopyridyl)	$-CF_3$
E106 (a, b, c, and d)	-2-(3-cyanopyridyl)	$-OCF_3$
E107 (a, b, c, and d)	-2-(3-cyanopyridyl)	-Cl
E108 (a, b, c, and d)	-2-(3-cyanopyridyl)	-Br
E109 (a, b, c, and d)	-2-(3-cyanopyridyl)	-I
E110 (a, b, c, and d)	-2-(3-cyanopyridyl)	-n-butyl
E111 (a, b, c, and d)	-2-(3-cyanopyridyl)	-n-propyl
E112 (a, b, c, and d)	-2-(3-cyanopyridyl)	-isopropyl
E113 (a, b, c, and d)	-2-(3-bromopyridyl)	-t-butyl
E114 (a, b, c, and d)	-2-(3-bromopyridyl)	-iso-butyl
E115 (a, b, c, and d)	-2-(3-bromopyridyl)	-sec-butyl
E116 (a, b, c, and d)	-2-(3-bromopyridyl)	-cyclohexyl
E117 (a, b, c, and d)	-2-(3-bromopyridyl)	-t-butoxy
E118 (a, b, c, and d)	-2-(3-bromopyridyl)	-isopropoxy
E119 (a, b, c, and d)	-2-(3-bromopyridyl)	$-CF_3$
E120 (a, b, c, and d)	-2-(3-bromopyridyl)	$-OCF_3$
E121 (a, b, c, and d)	-2-(3-bromopyridyl)	-Cl
E122 (a, b, c, and d)	-2-(3-bromopyridyl)	-Br
E123 (a, b, c, and d)	-2-(3-bromopyridyl)	-I
E124 (a, b, c, and d)	-2-(3-bromopyridyl)	-n-butyl
E125 (a, b, c, and d)	-2-(3-bromopyridyl)	-n-propyl
E126 (a, b, c, and d)	-2-(3-bromopyridyl)	-iso-propyl
E127 (a, b, c, and d)	-2-(3-iodopyridyl)	-t-butyl

E128 (a, b, c, and d)	-2-(3-iodopyridyl)	-iso-butyl
E129 (a, b, c, and d)	-2-(3-iodopyridyl)	-sec-butyl
E130 (a, b, c, and d)	-2-(3-iodopyridyl)	-cyclohexyl
E131 (a, b, c, and d)	-2-(3-iodopyridyl)	-t-butoxy
E132 (a, b, c, and d)	-2-(3-iodopyridyl)	-isopropoxy
E133 (a, b, c, and d)	-2-(3-iodopyridyl)	$-CF_3$
E134 (a, b, c, and d)	-2-(3-iodopyridyl)	$-OCF_3$
E135 (a, b, c, and d)	-2-(3-iodopyridyl)	-Cl
E136 (a, b, c, and d)	-2-(3-iodopyridyl)	-Br
E137 (a, b, c, and d)	-2-(3-iodopyridyl)	-I
E138 (a, b, c, and d)	-2-(3-iodopyridyl)	-n-butyl
E139 (a, b, c, and d)	-2-(3-iodopyridyl)	-n-propyl
E140 (a, b, c, and d)	-2-(3-iodopyridyl)	-iso-propyl
E141 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-t-butyl
E142 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-iso-butyl
E143 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-sec-butyl
E144 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-cyclohexyl
E145 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-t-butoxy
E146 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-isopropoxy
E147 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	$-CF_3$
E148 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	$-OCF_3$
E149 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-Cl
E150 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-Br
E151 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-I
E152 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-n-butyl
E153 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-n-propyl
E154 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-iso-propyl
E155 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-t-butyl
E156 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-iso-butyl
E157 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-sec-butyl
E158 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-cyclohexyl
E159 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-t-butoxy
E160 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-isopropoxy
E161 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	$-CF_3$
E162 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	$-OCF_3$

E163 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-Cl
E164 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-Br
E165 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-I
E166 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-n-butyl
E167 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-n-propyl
E168 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-iso-propyl
E169 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-t-butyl
E170 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-iso-butyl
E171 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-sec-butyl
E172 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-cyclohexyl
E173 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-t-butoxy
E174 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-isopropoxy
E175 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	$-CF_3$
E176 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	$-OCF_3$
E177 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-Cl
E178 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-Br
E179 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-I
E180 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-n-butyl
E181 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-n-propyl
E182 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-iso-propyl
E183 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-t-butyl
E184 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-iso-butyl
E185 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-sec-butyl
E186 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-cyclohexyl
E187 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-t-butoxy
E188 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-isopropoxy
E189 (a, b, c, and d)	-2-(3-chloropyrazinyl)	$-CF_3$
E190 (a, b, c, and d)	-2-(3-chloropyrazinyl)	$-OCF_3$
E191 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-Cl
E192 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-Br
E193 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-I
E194 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-n-butyl
E195 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-n-propyl
E196 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-iso-propyl
E197 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-t-butyl

E198 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-iso-butyl
E199 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-sec-butyl
E200 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-cyclohexyl
E201 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-t-butoxy
E202 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-isopropoxy
E203 (a, b, c, and d)	-2-(3-methylpyrazinyl)	$-CF_3$
E204 (a, b, c, and d)	-2-(3-methylpyrazinyl)	$-OCF_3$
E205 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-Cl
E206 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-Br
E207 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-I
E208 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-n-butyl
E209 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-n-propyl
E210 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-iso-propyl
E211 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-t-butyl
E212 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-iso-butyl
E213 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-sec-butyl
E214 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-cyclohexyl
E215 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-t-butoxy
E216 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-isopropoxy
E217 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	$-CF_3$
E218 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	$-OCF_3$
E219 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-Cl
E220 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-Br
E221 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-I
E222 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-n-butyl
E223 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-n-propyl
E224 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-iso-propyl
E225 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-t-butyl
E226 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-iso-butyl
E227 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-sec-butyl
E228 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-cyclohexyl
E229 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-t-butoxy
E230 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-isopropoxy
E231 (a, b, c, and d)	-3-(4-chloropyridazinyl)	$-CF_3$
E232 (a, b, c, and d)	-3-(4-chloropyridazinyl)	$-OCF_3$

E233 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-Cl
E234 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-Br
E235 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-I
E236 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-n-butyl
E237 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-n-propyl
E238 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-iso-propyl
E239 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-t-butyl
E240 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-iso-butyl
E241 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-sec-butyl
E242 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-cyclohexyl
E243 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-t-butoxy
E244 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-isopropoxy
E245 (a, b, c, and d)	-3-(4-methylpyridazinyl)	$-CF_3$
E246 (a, b, c, and d)	-3-(4-methylpyridazinyl)	$-OCF_3$
E247 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-Cl
E248 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-Br
E249 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-I
E250 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-n-butyl
E251 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-n-propyl
E252 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-iso-propyl
E253 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-t-butyl
E254 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-iso-butyl
E255 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-sec-butyl
E256 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-cyclohexyl
E257 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-t-butoxy
E258 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-isopropoxy
E259 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	$-CF_3$
E260 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	$-OCF_3$
E261 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-Cl
E262 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-Br
E263 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-I
E264 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-n-butyl
E265 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-n-propyl
E266 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-iso-propyl
E267 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-t-butyl

E268 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-iso-butyl
E269 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-sec-butyl
E270 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-cyclohexyl
E271 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-t-butoxy
E272 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-isopropoxy
E273 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	$-CF_3$
E274 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	$-OCF_3$
E275 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-Cl
E276 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-Br
E277 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-I
E278 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-n-butyl
E279 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-n-propyl
E280 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-iso-propyl
E281 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-t-butyl
E282 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-iso-butyl
E283 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-sec-butyl
E284 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-cyclohexyl
E285 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-t-butoxy
E286 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-isopropoxy
E287 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	$-CF_3$
E288 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	$-OCF_3$
E289 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-Cl
E290 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-Br
E291 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-I
E292 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-n-butyl
E293 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-n-propyl
E294 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-iso-propyl
E295 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-t-butyl
E296 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-iso-butyl
E297 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-sec-butyl
E298 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-cyclohexyl
E299 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-t-butoxy
E300 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-isopropoxy
E301 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	$-CF_3$
E302 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	$-OCF_3$

E303 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-Cl
E304 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-Br
E305 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-I
E306 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-n-butyl
E307 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-n-propyl
E308 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-iso-propyl

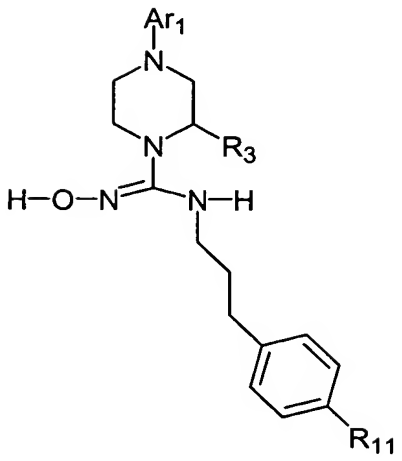
"a" means R_3 is -H.

"b" means R_3 is $-CH_3$ and the Hydroxyiminopiperazine Compound is racemic.

"c" means R_3 is $-CH_3$ and the carbon atom to which R_3 is attached is in the (R) configuration.

"d" means R_3 is $-CH_3$ and the carbon atom to which R_3 is attached is in the (S) configuration.

Table VI



and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar_1	R_{11}
F1 (a, b, c, and d)	-2-(3-chloropyridyl)	-t-butyl
F2 (a, b, c, and d)	-2-(3-chloropyridyl)	-iso-butyl
F3 (a, b, c, and d)	-2-(3-chloropyridyl)	-sec-butyl
F4 (a, b, c, and d)	-2-(3-chloropyridyl)	-cyclohexyl
F5 (a, b, c, and d)	-2-(3-chloropyridyl)	-t-butoxy
F6 (a, b, c, and d)	-2-(3-chloropyridyl)	-isopropoxy
F7 (a, b, c, and d)	-2-(3-chloropyridyl)	$-CF_3$
F8 (a, b, c, and d)	-2-(3-chloropyridyl)	$-OCF_3$
F9 (a, b, c, and d)	-2-(3-chloropyridyl)	-Cl
F10 (a, b, c, and d)	-2-(3-chloropyridyl)	-Br
F11 (a, b, c, and d)	-2-(3-chloropyridyl)	-I
F12 (a, b, c, and d)	-2-(3-chloropyridyl)	-n-butyl
F13 (a, b, c, and d)	-2-(3-chloropyridyl)	-n-propyl
F14 (a, b, c, and d)	-2-(3-chloropyridyl)	-iso-propyl
F15 (a, b, c, and d)	-2-(3-fluoropyridyl)	-t-butyl
F16 (a, b, c, and d)	-2-(3-fluoropyridyl)	-iso-butyl
F17 (a, b, c, and d)	-2-(3-fluoropyridyl)	-sec-butyl
F18 (a, b, c, and d)	-2-(3-fluoropyridyl)	-cyclohexyl
F19 (a, b, c, and d)	-2-(3-fluoropyridyl)	-t-butoxy
F20 (a, b, c, and d)	-2-(3-fluoropyridyl)	-isopropoxy
F21 (a, b, c, and d)	-2-(3-fluoropyridyl)	$-CF_3$
F22 (a, b, c, and d)	-2-(3-fluoropyridyl)	$-OCF_3$

F23 (a, b, c, and d)	-2-(3-fluoropyridyl)	-Cl
F24 (a, b, c, and d)	-2-(3-fluoropyridyl)	-Br
F25 (a, b, c, and d)	-2-(3-fluoropyridyl)	-I
F26 (a, b, c, and d)	-2-(3-fluoropyridyl)	-n-butyl
F27 (a, b, c, and d)	-2-(3-fluoropyridyl)	-n-propyl
F28 (a, b, c, and d)	-2-(3-fluoropyridyl)	-iso-propyl
F29 (a, b, c, and d)	-2-(3-methylpyridyl)	-t-butyl
F30 (a, b, c, and d)	-2-(3-methylpyridyl)	-iso-butyl
F31 (a, b, c, and d)	-2-(3-methylpyridyl)	-sec-butyl
F32 (a, b, c, and d)	-2-(3-methylpyridyl)	-cyclohexyl
F33 (a, b, c, and d)	-2-(3-methylpyridyl)	-t-butoxy
F34 (a, b, c, and d)	-2-(3-methylpyridyl)	-isopropoxy
F35 (a, b, c, and d)	-2-(3-methylpyridyl)	$-CF_3$
F36 (a, b, c, and d)	-2-(3-methylpyridyl)	$-OCF_3$
F37 (a, b, c, and d)	-2-(3-methylpyridyl)	-Cl
F38 (a, b, c, and d)	-2-(3-methylpyridyl)	-Br
F39 (a, b, c, and d)	-2-(3-methylpyridyl)	-I
F40 (a, b, c, and d)	-2-(3-methylpyridyl)	-n-butyl
F41 (a, b, c, and d)	-2-(3-methylpyridyl)	-n-propyl
F42 (a, b, c, and d)	-2-(3-methylpyridyl)	-iso-propyl
F43 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-t-butyl
F44 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-iso-butyl
F45 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-sec-butyl
F46 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-cyclohexyl
F47 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-t-butoxy
F48 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-isopropoxy
F49 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	$-CF_3$
F50 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	$-OCF_3$
F51 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-Cl
F52 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-Br
F53 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-I
F54 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-n-butyl
F55 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-n-propyl
F56 (a, b, c, and d)	-2-(3-CF_3-pyridyl)	-iso-propyl
F57 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-t-butyl

F58 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-iso-butyl
F59 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-sec-butyl
F60 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-cyclohexyl
F61 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-t-butoxy
F62 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-isopropoxy
F63 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-CF_3
F64 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-OCF_3
F65 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-Cl
F66 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-Br
F67 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-I
F68 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-n-butyl
F69 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-n-propyl
F70 (a, b, c, and d)	-2-(3-CHF_2-pyridyl)	-iso-propyl
F71 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-t-butyl
F72 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-iso-butyl
F73 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-sec-butyl
F74 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-cyclohexyl
F75 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-t-butoxy
F76 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-isopropoxy
F77 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-CF_3
F78 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-OCF_3
F79 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-Cl
F80 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-Br
F81 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-I
F82 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-n-butyl
F83 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-n-propyl
F84 (a, b, c, and d)	-2-(3-hydroxypyridyl)	-iso-propyl
F85 (a, b, c, and d)	-2-(3-nitropyridyl)	-t-butyl
F86 (a, b, c, and d)	-2-(3-nitropyridyl)	-iso-butyl
F87 (a, b, c, and d)	-2-(3-nitropyridyl)	-sec-butyl
F88 (a, b, c, and d)	-2-(3-nitropyridyl)	-cyclohexyl
F89 (a, b, c, and d)	-2-(3-nitropyridyl)	-t-butoxy
F90 (a, b, c, and d)	-2-(3-nitropyridyl)	-isopropoxy
F91 (a, b, c, and d)	-2-(3-nitropyridyl)	-CF_3
F92 (a, b, c, and d)	-2-(3-nitropyridyl)	-OCF_3

F93 (a, b, c, and d)	-2-(3-nitropyridyl)	-Cl
F94 (a, b, c, and d)	-2-(3-nitropyridyl)	-Br
F95 (a, b, c, and d)	-2-(3-nitropyridyl)	-I
F96 (a, b, c, and d)	-2-(3-nitropyridyl)	-n-butyl
F97 (a, b, c, and d)	-2-(3-nitropyridyl)	-n-propyl
F98 (a, b, c, and d)	-2-(3-nitropyridyl)	-iso-propyl
F99 (a, b, c, and d)	-2-(3-cyanopyridyl)	-t-butyl
F100 (a, b, c, and d)	-2-(3-cyanopyridyl)	-iso-butyl
F101 (a, b, c, and d)	-2-(3-cyanopyridyl)	-sec-butyl
F102 (a, b, c, and d)	-2-(3-cyanopyridyl)	-cyclohexyl
F103 (a, b, c, and d)	-2-(3-cyanopyridyl)	-t-butoxy
F104 (a, b, c, and d)	-2-(3-cyanopyridyl)	-isopropoxy
F105 (a, b, c, and d)	-2-(3-cyanopyridyl)	$-CF_3$
F106 (a, b, c, and d)	-2-(3-cyanopyridyl)	$-OCF_3$
F107 (a, b, c, and d)	-2-(3-cyanopyridyl)	-Cl
F108 (a, b, c, and d)	-2-(3-cyanopyridyl)	-Br
F109 (a, b, c, and d)	-2-(3-cyanopyridyl)	-I
F110 (a, b, c, and d)	-2-(3-cyanopyridyl)	-n-butyl
F111 (a, b, c, and d)	-2-(3-cyanopyridyl)	-n-propyl
F112 (a, b, c, and d)	-2-(3-cyanopyridyl)	-isopropyl
F113 (a, b, c, and d)	-2-(3-bromopyridyl)	-t-butyl
F114 (a, b, c, and d)	-2-(3-bromopyridyl)	-iso-butyl
F115 (a, b, c, and d)	-2-(3-bromopyridyl)	-sec-butyl
F116 (a, b, c, and d)	-2-(3-bromopyridyl)	-cyclohexyl
F117 (a, b, c, and d)	-2-(3-bromopyridyl)	-t-butoxy
F118 (a, b, c, and d)	-2-(3-bromopyridyl)	-isopropoxy
F119 (a, b, c, and d)	-2-(3-bromopyridyl)	$-CF_3$
F120 (a, b, c, and d)	-2-(3-bromopyridyl)	$-OCF_3$
F121 (a, b, c, and d)	-2-(3-bromopyridyl)	-Cl
F122 (a, b, c, and d)	-2-(3-bromopyridyl)	-Br
F123 (a, b, c, and d)	-2-(3-bromopyridyl)	-I
F124 (a, b, c, and d)	-2-(3-bromopyridyl)	-n-butyl
F125 (a, b, c, and d)	-2-(3-bromopyridyl)	-n-propyl
F126 (a, b, c, and d)	-2-(3-bromopyridyl)	-iso-propyl
F127 (a, b, c, and d)	-2-(3-iodopyridyl)	-t-butyl

F128 (a, b, c, and d)	-2-(3-iodopyridyl)	-iso-butyl
F129 (a, b, c, and d)	-2-(3-iodopyridyl)	-sec-butyl
F130 (a, b, c, and d)	-2-(3-iodopyridyl)	-cyclohexyl
F131 (a, b, c, and d)	-2-(3-iodopyridyl)	-t-butoxy
F132 (a, b, c, and d)	-2-(3-iodopyridyl)	-isopropoxy
F133 (a, b, c, and d)	-2-(3-iodopyridyl)	$-CF_3$
F134 (a, b, c, and d)	-2-(3-iodopyridyl)	$-OCF_3$
F135 (a, b, c, and d)	-2-(3-iodopyridyl)	-Cl
F136 (a, b, c, and d)	-2-(3-iodopyridyl)	-Br
F137 (a, b, c, and d)	-2-(3-iodopyridyl)	-I
F138 (a, b, c, and d)	-2-(3-iodopyridyl)	-n-butyl
F139 (a, b, c, and d)	-2-(3-iodopyridyl)	-n-propyl
F140 (a, b, c, and d)	-2-(3-iodopyridyl)	-iso-propyl
F141 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-t-butyl
F142 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-iso-butyl
F143 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-sec-butyl
F144 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-cyclohexyl
F145 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-t-butoxy
F146 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-isopropoxy
F147 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	$-CF_3$
F148 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	$-OCF_3$
F149 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-Cl
F150 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-Br
F151 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-I
F152 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-n-butyl
F153 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-n-propyl
F154 (a, b, c, and d)	-4-(5-chloropyrimidinyl)	-iso-propyl
F155 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-t-butyl
F156 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-iso-butyl
F157 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-sec-butyl
F158 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-cyclohexyl
F159 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-t-butoxy
F160 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-isopropoxy
F161 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	$-CF_3$
F162 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	$-OCF_3$

F163 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-Cl
F164 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-Br
F165 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-I
F166 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-n-butyl
F167 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-n-propyl
F168 (a, b, c, and d)	-4-(5-methylpyrimidinyl)	-iso-propyl
F169 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-t-butyl
F170 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-iso-butyl
F171 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-sec-butyl
F172 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-cyclohexyl
F173 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-t-butoxy
F174 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-isopropoxy
F175 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	$-CF_3$
F176 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	$-OCF_3$
F177 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-Cl
F178 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-Br
F179 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-I
F180 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-n-butyl
F181 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-n-propyl
F182 (a, b, c, and d)	-4-(5-fluoropyrimidinyl)	-iso-propyl
F183 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-t-butyl
F184 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-iso-butyl
F185 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-sec-butyl
F186 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-cyclohexyl
F187 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-t-butoxy
F188 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-isopropoxy
F189 (a, b, c, and d)	-2-(3-chloropyrazinyl)	$-CF_3$
F190 (a, b, c, and d)	-2-(3-chloropyrazinyl)	$-OCF_3$
F191 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-Cl
F192 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-Br
F193 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-I
F194 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-n-butyl
F195 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-n-propyl
F196 (a, b, c, and d)	-2-(3-chloropyrazinyl)	-iso-propyl
F197 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-t-butyl

F198 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-iso-butyl
F199 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-sec-butyl
F200 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-cyclohexyl
F201 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-t-butoxy
F202 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-isopropoxy
F203 (a, b, c, and d)	-2-(3-methylpyrazinyl)	$-CF_3$
F204 (a, b, c, and d)	-2-(3-methylpyrazinyl)	$-OCF_3$
F205 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-Cl
F206 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-Br
F207 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-I
F208 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-n-butyl
F209 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-n-propyl
F210 (a, b, c, and d)	-2-(3-methylpyrazinyl)	-iso-propyl
F211 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-t-butyl
F212 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-iso-butyl
F213 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-sec-butyl
F214 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-cyclohexyl
F215 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-t-butoxy
F216 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-isopropoxy
F217 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	$-CF_3$
F218 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	$-OCF_3$
F219 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-Cl
F220 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-Br
F221 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-I
F222 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-n-butyl
F223 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-n-propyl
F224 (a, b, c, and d)	-2-(3-fluoropyrazinyl)	-iso-propyl
F225 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-t-butyl
F226 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-iso-butyl
F227 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-sec-butyl
F228 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-cyclohexyl
F229 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-t-butoxy
F230 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-isopropoxy
F231 (a, b, c, and d)	-3-(4-chloropyridazinyl)	$-CF_3$
F232 (a, b, c, and d)	-3-(4-chloropyridazinyl)	$-OCF_3$

F233 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-Cl
F234 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-Br
F235 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-I
F236 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-n-butyl
F237 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-n-propyl
F238 (a, b, c, and d)	-3-(4-chloropyridazinyl)	-iso-propyl
F239 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-t-butyl
F240 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-iso-butyl
F241 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-sec-butyl
F242 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-cyclohexyl
F243 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-t-butoxy
F244 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-isopropoxy
F245 (a, b, c, and d)	-3-(4-methylpyridazinyl)	$-CF_3$
F246 (a, b, c, and d)	-3-(4-methylpyridazinyl)	$-OCF_3$
F247 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-Cl
F248 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-Br
F249 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-I
F250 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-n-butyl
F251 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-n-propyl
F252 (a, b, c, and d)	-3-(4-methylpyridazinyl)	-iso-propyl
F253 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-t-butyl
F254 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-iso-butyl
F255 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-sec-butyl
F256 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-cyclohexyl
F257 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-t-butoxy
F258 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-isopropoxy
F259 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	$-CF_3$
F260 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	$-OCF_3$
F261 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-Cl
F262 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-Br
F263 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-I
F264 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-n-butyl
F265 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-n-propyl
F266 (a, b, c, and d)	-3-(4-fluoropyridazinyl)	-iso-propyl
F267 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-t-butyl

F268 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-iso-butyl
F269 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-sec-butyl
F270 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-cyclohexyl
F271 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-t-butoxy
F272 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-isopropoxy
F273 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	$-CF_3$
F274 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	$-OCF_3$
F275 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-Cl
F276 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-Br
F277 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-I
F278 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-n-butyl
F279 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-n-propyl
F280 (a, b, c, and d)	-5-(4-chlorothiadiazolyl)	-iso-propyl
F281 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-t-butyl
F282 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-iso-butyl
F283 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-sec-butyl
F284 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-cyclohexyl
F285 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-t-butoxy
F286 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-isopropoxy
F287 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	$-CF_3$
F288 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	$-OCF_3$
F289 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-Cl
F290 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-Br
F291 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-I
F292 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-n-butyl
F293 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-n-propyl
F294 (a, b, c, and d)	-5-(4-methylthiadiazolyl)	-iso-propyl
F295 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-t-butyl
F296 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-iso-butyl
F297 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-sec-butyl
F298 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-cyclohexyl
F299 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-t-butoxy
F300 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-isopropoxy
F301 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	$-CF_3$
F302 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	$-OCF_3$

F303 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-Cl
F304 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-Br
F305 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-I
F306 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-n-butyl
F307 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-n-propyl
F308 (a, b, c, and d)	-5-(4-fluorothiadiazolyl)	-iso-propyl

"a" means R_3 is -H.

"b" means R_3 is $-CH_3$ and the Hydroxyiminopiperazine Compound is racemic.

"c" means R_3 is $-CH_3$ and the carbon atom to which R_3 is attached is in the (R) configuration.

"d" means R_3 is $-CH_3$ and the carbon atom to which R_3 is attached is in the (S) configuration.

4.9 Definitions

As used herein, the terms used above having following meaning:

"-(C_1-C_{10})alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative straight chain -(C_1-C_{10})alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl, and -n-decyl. Representative branched -(C_1-C_{10})alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,2-dimethylhexyl, 1,3-dimethylhexyl, 3,3-dimethylhexyl, 1,2-dimethylheptyl, 1,3-dimethylheptyl, and 3,3-dimethylheptyl.

"-(C_1-C_6)alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms. Representative straight chain -(C_1-C_6)alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl. Representative branched -(C_1-C_6)alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethtylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, and 3,3-dimethylbutyl.

"-(C_2-C_{10})alkenyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C_2-C_{10})alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl, -1-nonenyl, -2-nonenyl, -3-nonenyl, -1-decenyl, -2-decenyl, -3-decenyl and the like.

"-(C_2-C_6)alkenyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C_2-C_6)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, 2-hexenyl, 3-hexenyl and the like.

"-(C_2-C_{10})alkynyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at lease one carbon-carbon triple bond. Representative straight chain and branched -(C_2-C_{10})alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl, -1-heptynyl, -2-heptynyl, -6-heptynyl, -1-octynyl, -2-octynyl, -7-octynyl, -1-nonynyl, -2-nonynyl, -8-nonynyl, -1-decynyl, -2-decynyl, -9-decynyl and the like.

"-(C_2-C_6)alkynyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at lease one carbon-carbon triple bond. Representative straight chain and branched (C_2-C_6)alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl and the like.

"-(C_3-C_{10})cycloalkyl" means a saturated cyclic hydrocarbon having from 3 to 10 carbon atoms. Representative (C_3-C_{10})cycloalkyls are -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -cyclononyl, and -cyclodecyl.

"-(C_3-C_8)cycloalkyl" means a saturated cyclic hydrocarbon having from 3 to 8 carbon atoms. Representative (C_3-C_8)cycloalkyls include -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, and -cyclooctyl.

"-(C_8-C_{14})bicycloalkyl" means a bi-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated cyclic alkyl ring. Representative -(C_8-C_{14})bicycloalkyls include -indanyl, -1,2,3,4-tetrahydronaphthyl, -5,6,7,8-tetrahydronaphthyl, -perhydronaphthyl and the like.

"-(C_8-C_{14})tricycloalkyl" means a tri-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated cyclic ring. Representative -(C_8-C_{14})tricycloalkyls include -pyrenyl, -1,2,3,4-tetrahydroanthracenyl, -perhydroanthracenyl -aceanthreneyl, -1,2,3,4-tetrahydropenanthrenyl, -5,6,7,8-tetrahydrophenanthrenyl, -perhydrophenanthrenyl and the like.

"-(C_5-C_{10})cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 10 carbon atoms. Representative (C_5-C_{10})cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl,-cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl and the like.

"-(C_5-C_8)cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 8 carbon atoms. Representative (C_5-C_8)cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl, -cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl and the like.

"-(C_8-C_{14})bicycloalkenyl" means a bi-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 8 to 14 carbon atoms. Representative -(C_8-C_{14})bicycloalkenyls include -indenyl, -pentalenyl, -naphthalenyl, -azulenyl, -heptalenyl, -1,2,7,8-tetrahydronaphthalenyl and the like.

"-(C_8-C_{14})tricycloalkenyl" means a tri-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 8 to 14 carbon atoms. Representative -(C_8-C_{14})tricycloalkenyls include -anthracenyl, -phenanthrenyl, -phenalenyl, -acenaphthalenyl, *as*-indacenyl, *s*-indacenyl and the like.

"-(3- to 7-membered)heterocycle" or "-(3- to 7-membered)heterocyclo" means a 3- to 7-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 3-membered -(3- to 7-membered)heterocycle can contain up to 3 heteroatoms, and a 4- to 7-membered -(3- to 7-membered)heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(3- to 7-membered)heterocycle can be attached via a nitrogen, sulfur, or carbon atom. Representative -(3- to 7-membered)heterocycles include pyridyl, furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, thiadiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl and the like.

"-(3- to 5-membered)heterocycle" or "-(3- to 5-membered)heterocyclo" means a 3- to 5-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 3-membered -(3- to 5-membered)heterocycle can contain up to 3 heteroatoms, and a 4- to 5-membered -(3- to 5-membered)heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(3- to 5-membered)heterocycle can be attached via a nitrogen, sulfur, or carbon atom. Representative -(3- to 5-membered)heterocycles include furyl, thiophenyl, pyrrolyl,

oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, triazinyl, pyrrolidinonyl, pyrrolidinyl, hydantoinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl and the like.

"-(7- to 10-membered)bicycloheterocycle" or "-(7- to 10-membered)bicycloheterocyclo" means a 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A -(7- to 10-membered)bicycloheterocycle contains from 1 to 4 heteroatoms independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(7- to 10-membered)bicycloheterocycle can be attached via a nitrogen, sulfur, or carbon atom. Representative -(7- to 10-membered)bicycloheterocycles include -quinolinyl, -isoquinolinyl, -chromonyl, -coumarinyl, -indolyl, -indolizinyl, -benzo[b]furanyl, -benzo[b]thiophenyl, -indazolyl, -purinyl, -4H-quinolizinyl, -isoquinolyl, -quinolyl, -phthalazinyl, -naphthyridinyl, -carbazolyl, -β-carbolinyl and the like.

"-(C_{14})aryl" means a 14-membered aromatic carbocyclic moiety such as -anthryl or -phenanthryl.

"-(5- to 10-membered)heteroaryl" means an aromatic heterocycle ring of 5 to 10 members, including both mono- and bicyclic ring systems, wherein at least one carbon atom of one or both of the rings is replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur. One or both of the -(5- to 10-membered)heteroaryl's rings contain at least one carbon atom. Representative -(5- to 10-membered)heteroaryls include pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

"-CH_2(halo)" means a methyl group wherein one of the hydrogens of the methyl group has been replaced with a halogen. Representative -CH_2(halo) groups include -CH_2F, -CH_2Cl, -CH_2Br, and -CH_2I.

"-CH(halo)$_2$" means a methyl group wherein two of the hydrogens of the methyl group have been replaced with a halogen. Representative -CH(halo)$_2$ groups include -CHF_2, -$CHCl_2$, -$CHBr_2$, CHBrCl, CHClI, and -CHI_2.

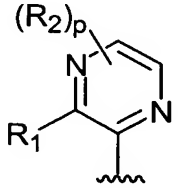
"-C(halo)$_3$" means a methyl group wherein each of the hydrogens of the methyl group has been replaced with a halogen. Representative -C(halo)$_3$ groups include -CF_3, -CCl_3, -CBr_3, and -CI_3.

"-Halogen" or "-Halo" means -F, -Cl, -Br, or -I.

The phrase "pyridyl group" means

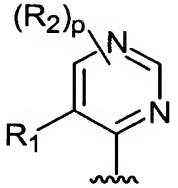
wherein R_1, R_2, and n are defined above for the Hydroxyiminopiperazine Compounds of formula (I).

The phrase "pyrazinyl group" means,



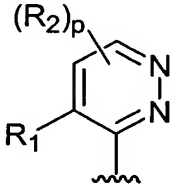
wherein R_1, R_2, and p are defined above for the Hydroxyiminopiperazine Compounds of formula (II).

The phrase "pyrimidinyl group" means



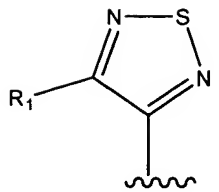
wherein R_1, R_2, and p are defined above for the Hydroxyiminopiperazine Compounds of formula (III).

The phrase "pyridazinyl group" means



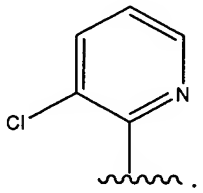
wherein R_1, R_2, and p are defined above for the Hydroxyiminopiperazine Compounds of formula (IV).

The phrase "thiadiazolyl group" means

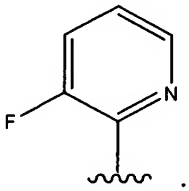


wherein R_1 is defined above for the Hydroxyiminopiperazine Compounds of formula (I)-(VI).

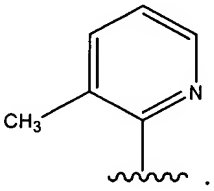
The phrase "2-(3-chloropyridyl)" means



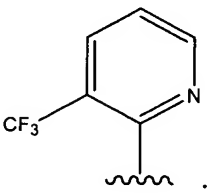
The phrase "2-(3-fluoropyridyl)" means



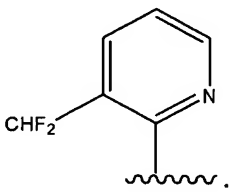
The phrase "2-(3-methylpyridyl)" means



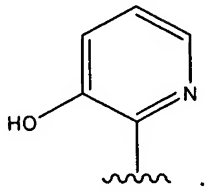
The phrase "2-(3-CF_3-methylpyridyl)" means



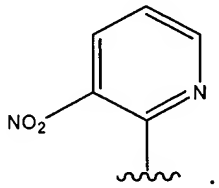
The phrase "2-(3-CHF_2-pyridyl)" means



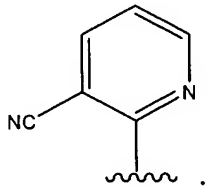
The phrase "2-(3-hydroxypyridyl)" means



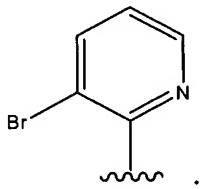
The phrase "2-(3-nitropyridyl)" means



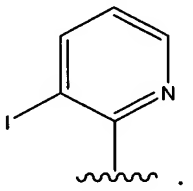
The phrase "2-(3-cyanopyridyl)" means



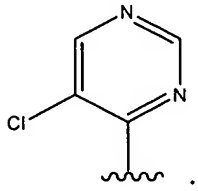
The phrase "2-(3-bromopyridyl)" means



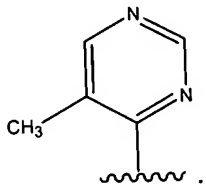
The phrase "2-(3-iodopyridyl)" means



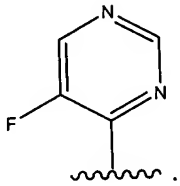
The phrase "4-(5-chloropyrimidinyl)" means



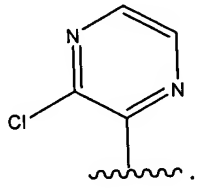
The phrase "4-(5-methylpyrimidinyl)" means



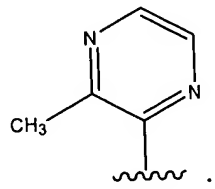
The phrase "4-(5-fluoropyrimidinyl)" means



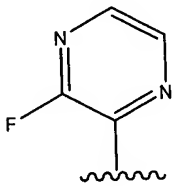
The phrase "2-(3-chloropyrazinyl)" means



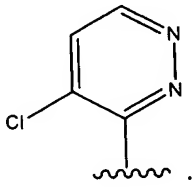
The phrase "2-(3-methylpyrazinyl)" means



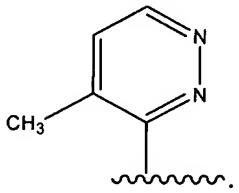
The phrase "2-(3-fluoropyrazinyl)" means



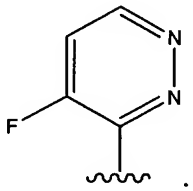
The phrase "3-(4-chloropyridazinyl)" means



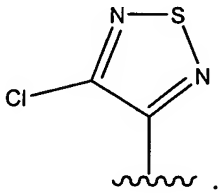
The phrase "3-(4-methylpyridazinyl)" means



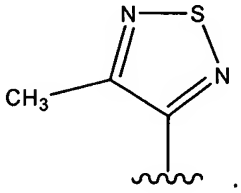
The phrase "3-(4-fluoropyridazinyl)" means



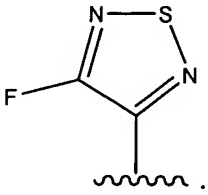
The phrase "5-(4-chlorothiadiazolyl)" means



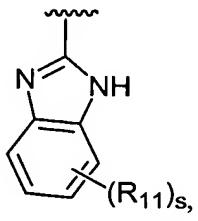
The phrase "5-(4-methylthiadiazolyl)" means



The phrase "5-(4-fluorothiadiazolyl)" means

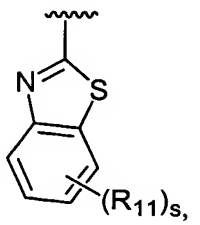


The phrase "benzoimidiazolyl group " means



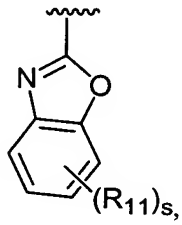
wherein R_{11} and s are defined above for the Hydroxyiminopiperazine Compounds of formula (VI) or (VII).

The phrase "benzothiazolyl group" means



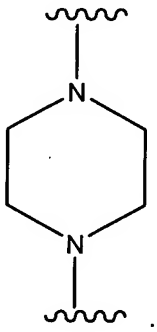
wherein R_{11} and s are defined above for the Hydroxyiminopiperazine Compounds of formula (VI) or (VII).

The phrase "benzooxazolyl group" means

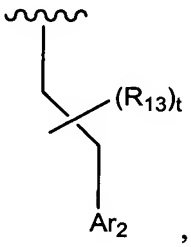


wherein R_{11} and s are defined above for the Hydroxyiminopiperazine Compounds of formula (VI) or (VII).

The phrase "piperazine ring" means

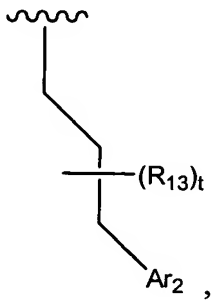


The phrase "phenethyl group" means an ethylene group attached to a terminal Ar_2 group, wherein one or each of two hydrogens of the ethylene group can be optionally substituted with an R_{13} group. A phenethyl group is depicted below:



wherein R_{13}, Ar_2, and t are defined above for the Hydroxyiminopiperazine Compounds of formula (VI).

The phrase "phenpropyl group" means an n-propylene group attached to a terminal Ar_2 group, wherein one or each of two hydrogens of the n-propylene group can be optionally substituted with an R_{13} group. A phenpropyl group is depicted below:



wherein R_{13}, Ar_2, and t are defined above for the Hydroxyiminopiperazine Compounds of formula (VII).

The term "animal," includes, but is not limited to, a cow, monkey, chimpanzee, baboon, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, guinea pig, and human.

The phrase "pharmaceutically acceptable salt," as used herein, is a salt formed from an acid and a basic functional group, such as a nitrogen group, of one of the Hydroxyiminopiperazine Compounds. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also refers to a salt formed from a Hydroxyiminopiperazine Compound having an acidic functional group, such as a carboxylic acid functional group, and an inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or

tris-(hydroxymethyl)methylamine, N,N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N,-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine and the like.

The phrase "effective amount," when used in connection with a Hydroxyiminopiperazine Compound means an amount effective for treating or preventing a Condition.

The phrase "effective amount," when used in connection with another therapeutic agent means an amount for providing the therapeutic effect of the therapeutic agent.

When a first group is "substituted with one or more" second groups, each of one or more of the first group's hydrogen atoms is replaced with a second group. In one embodiment, each carbon atom of a first group is independently substituted with one or two second groups. In another embodiment, each carbon atom of a first group is independently substituted with only one second group.

The term "UI" means urinary incontinence.

The term "IBD" means inflammatory-bowel disease.

The term "IBS" means irritable-bowel syndrome.

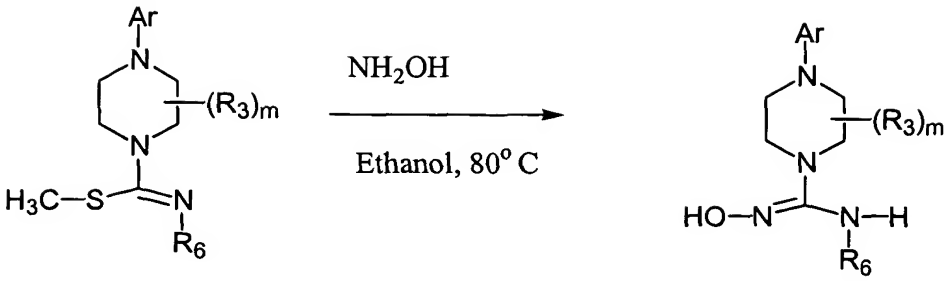
The term "ALS" means amyotrophic lateral sclerosis.

The phrases "treatment of," "treating," and the like include the amelioration or cessation of a Condition, or a symptom thereof.

The phrases "prevention of," "preventing," and the like include the avoidance of the onset of a Condition, or a symptom thereof.

4.10 Methods for Making the Hydroxyiminopiperazine Compounds

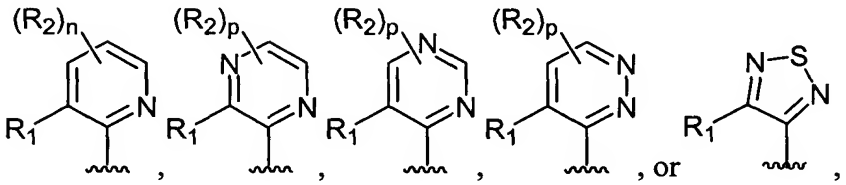
The Hydroxyiminopiperazine Compounds can be made using conventional organic synthesis including the following illustrative methods shown in the schemes below. The Hydroxyiminopiperazine Compounds wherein R_4 is -H can be obtained by the following illustrative method shown below in Scheme **A**:



A Hydroxyiminopiperazine Compound

Scheme A

wherein R_3, R_6, and m are defined above for the Hydroxyiminopiperazine Compounds and Ar is

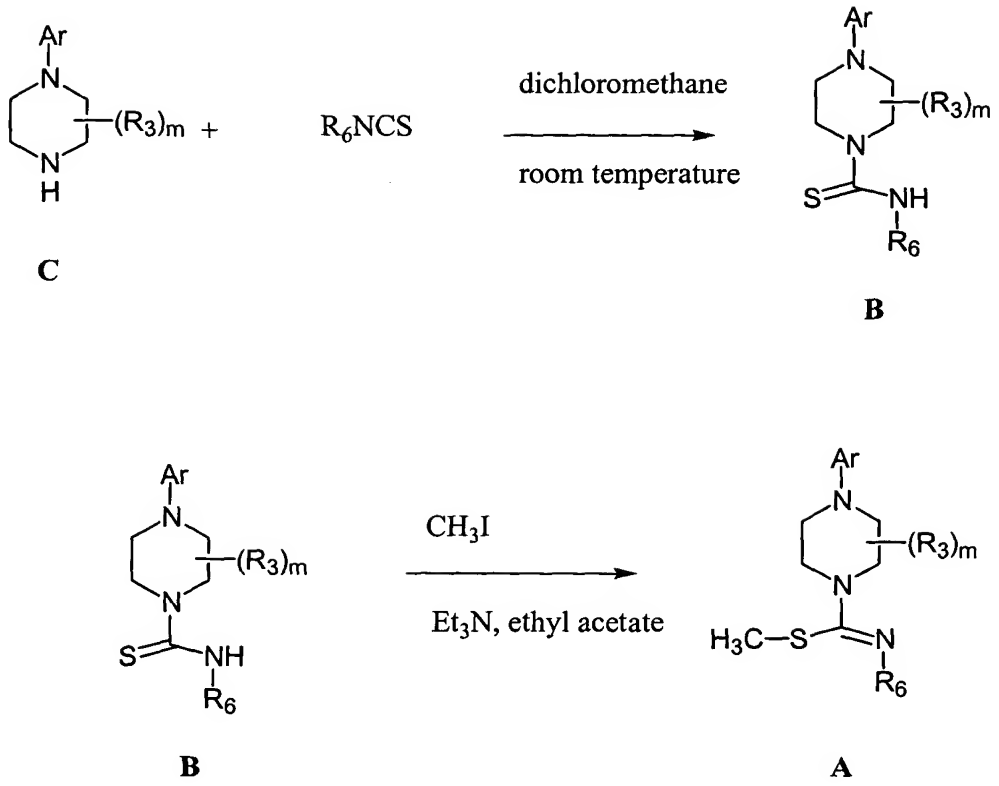


, , , , , or ,

wherein R_1, R_2, n, and p are defined above for the Hydroxyiminopiperazine Compounds of formulas (I)-(VII).

A compound of formula **A** (about 0.3 mmol) is reacted with hydroxylamine (50 weight percent in water, about 5.8 mmol) in about 1.5 mL of ethanol with stirring at a temperature of about 80°C for about 2 h. The mixture is then concentrated under reduced pressure to provide the Hydroximinopiperazine Compound, which can then be purified. In one embodiment, the Hydroximinopiperazine Compound is purified using column chromatography or recrystallization.

The compound of formula **A** can be obtained as shown below in Scheme **B**:



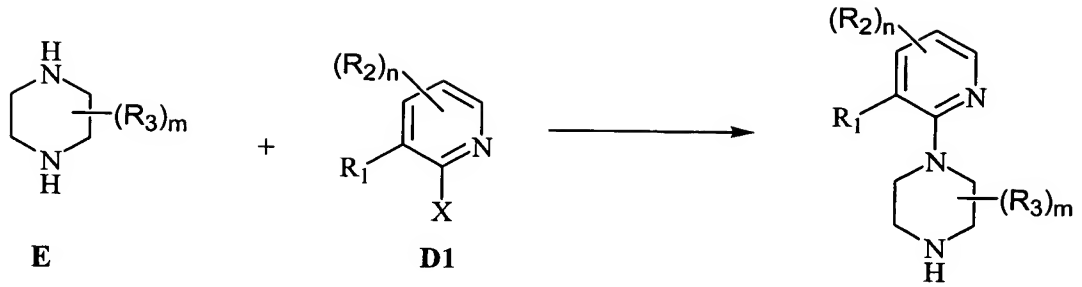
Scheme B

A solution of a compound of formula **C** (about 1 mmol) and isothiocyanate, R_6NCS, (about 1 mmol) in 1.5 mL of dichloromethane is stirred at room temperature for about 5 h. The resulting mixture is then concentrated under reduced pressure to provide the compound of formula **B**, which can then be purified. In one embodiment, the compound of formula **B** is purified using column chromatography or recrystallization. The compound of formula **B** (about 0.6 mmol) is then reacted with iodomethane (about 0.9 mmol) in about 3 mL of tetrahydrofuran with stirring at room temperature for about 12 h. Excess iodomethane is removed from the mixture using reduced pressure. A solution of triethylamine (about 1.74 mmol) in about 2.5 mL of ethyl acetate is then added to the mixture and the mixture is allowed to stir for about 2 h. The mixture is then concentrated under reduced pressure to provide the compound of formula **A**, which can then be purified. In one embodiment, the compound of formula **A** is purified using column chromatography or recrystallization.

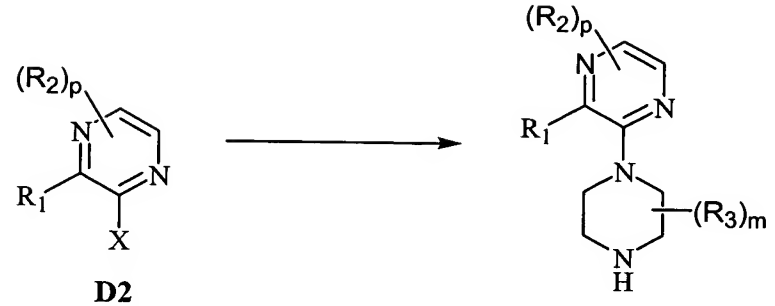
If the Ar group of the compound of formula **C** is substituted with a hydroxyl or amino group or $-R_3$ is a hydroxyl or amino group, the hydroxyl or amino group is protected using a suitable protecting group, using methods well known to those skilled in the art, before the compound of formula **C** is reacted with R_6NCS. Suitable protecting groups for hydroxyl group include, but are not limited to, methyl ether, methoxymethyl

ether, methoxythiomethyl ether, 2-methoxyethoxymethyl ether, bis(2-chloroethoxy)ethyl ether, tetrahydropyranyl ether, tetrahydrothiopyranyl ether, 4-methoxytetrahydropyranyl ether, methoxytetrahydrothiopyranyl ether, tetrahydrofuranyl ether, tetrahydrothiofuranyl ether, 1-ethoxyethyl ether, 1-methyl-1-methoxyethyl ether, 2-(phenylselenyl ether), *t*-butyl ether, allyl ether, benzyl ether, *o*-nitrobenzyl ether, triphenylmethyl ether, *o*-napthyldiphenylmethyl ether, *p*-methoxydiphenylmethyl ether, 9-(9-phenyl-10-oxo)anthryl ether (tritylone), trimethylsilyl ether, isopropyldimethylsilyl ether, *t*-butyldimethylsilyl ether, *t*-butyldiphenylsilyl ether, tribenzylsilyl ether, triisopropylsilyl ether, formate ester, acetate ester, trichloroacetate ester, phenoxyacetate ester, isobutyrate ester, pivaloate ester, adamantoate ester, benzoate ester, 2,4,6-trimethyl (mesitoate) ester, methyl carbonate, 2,2,2-trichlorocarbonate, allyl carbonate, p-nitrophenyl carbonate, benzyl carbonate, p-nitrobenzyl carbonate, S-benzylthiocarbonate, N-phenylcarbamate, nitrate ester, and 2,4-dinitrophenylsulfenate ester (*See, e.g.*, T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley-Interscience Publication, New York, (1981)). Suitable protecting groups for an amino group include, but are not limited to, 1,1-dimethyl-2,2,2-trichloroethyl carbamate, 1-methyl-1-(4-biphenylyl)ethyl carbamate, 2-trimethylsilylethyl carbamate, 9-fluorenylmethyl carbamate, and tert-butyl carbamate (T.W. Greene et al., *Protective Groups in Organic Synthesis*, 309-405 (2d ed. 1991)).

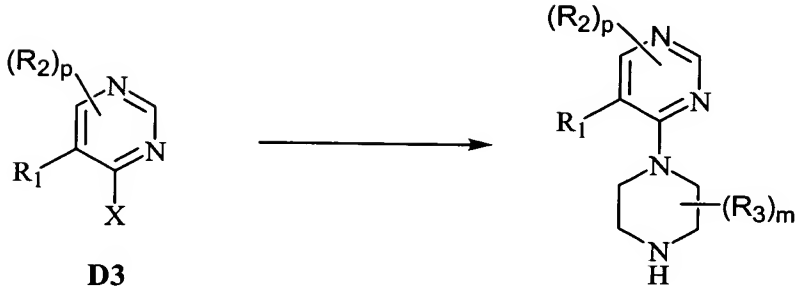
The compound of formula **C** can be obtained as shown below in Scheme **C**:



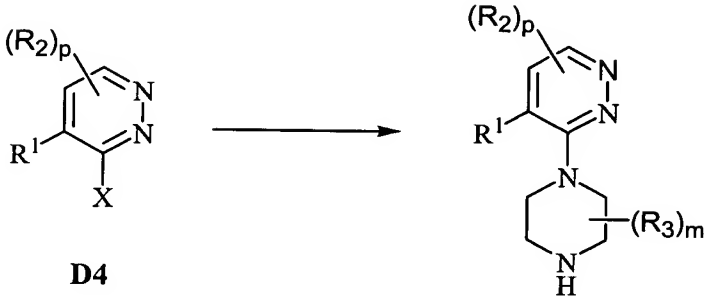
E **D1** **C1**



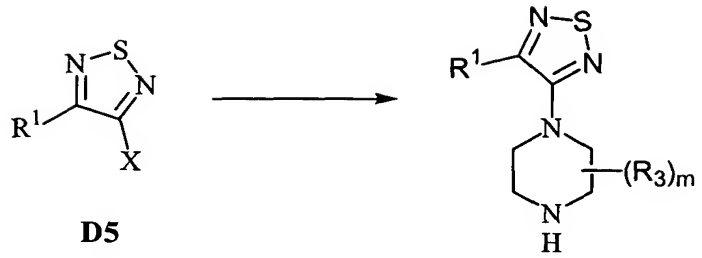
D2 **C2**



D3 **C3**



D4 **C4**



D5 **C5**

Scheme C

wherein R_1, R_2, R_3, m, n, and p are defined above for the Hydroxyiminopiperazine Compounds of formula (I) - (VII) and X is a halogen. In one embodiment, X is bromide, chloride, or iodide.

A compound of formula **D1-D5** (about 20 mmol) is reacted with a compound of formula **E** (about 27.5 mmol) in about 15 mL of dimethyl sulfoxide in the presence of triethylamine (about 30 mmol), optionally with heating, for about 24 h to provide a compound of formula **C**. The compound of formula **C** can be isolated from the reaction mixture and purified. In one embodiment, the compound of formula **C** is purified using column chromatography or recrystallization. If the compound of formula **E** is substituted with a hydroxyl or amino group, the hydroxyl or amino group can be protected using a suitable protecting group, using methods well known to those skilled in the art, before being reacted with a compound of formula **D1-D5**. Suitable protecting groups include, but are not limited to, those described above.

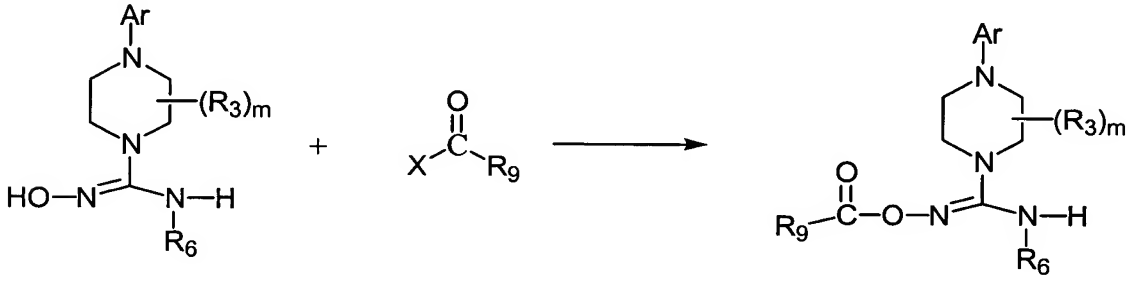
Compounds of formula **D** and **E** are commercially available or can be prepared by methods well known to those skilled in the art. The compound of formula **E** wherein m is 0 is commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com).

The isothiocyanantes, R_6NCS, are commercially available or can be prepared by methods well known to those skilled in the art (*See, e.g.*, J. March, *Advanced Organic Chemistry Reactions, Mechanisms, and Structure* 417, 429, 670, 904, and 930 (4th ed. 1992)).

The Hydroxyiminopiperazine Compounds wherein R_4 is -(C_1-C_{10})alkyl can be obtained by reacting a Hydroxyiminopiperazine Compound wherein R_4 is -H (about 0.2 mmol), that can be prepared as described above, dissolved in dimethylformamide (about 1.5 mL) with NaH (60 weight percent, about 0.21 mmol) with stirring for about 0.5 h. A -(C_1-C_{10})alkyl halide (about 0.2 mmol), for example, methyl iodide, is then added to the resulting

mixture and the mixture allowed to stir for about 4 h. The resulting mixture is then quenched with water, extracted with ethyl ether, the organic layer dried, and the solvent removed under reduced pressure to provide the Hydroxyiminopiperazine Compounds wherein R_4 is -(C_1-C_{10})alkyl. The Hydroxyiminopiperazine Compounds wherein R_4 is -(C_1-C_{10})alkyl can then be purified. In one embodiment, the Hydroxyiminopiperazine Compounds wherein R_4 is -(C_1-C_{10})alkyl is purified using column chromatography or recrystallization. If the Hydroxyiminopiperazine Compound wherein R_4 is -H is substituted with a hydroxyl or amino group, the hydroxyl or amino group is protected using a suitable protecting group, using methods well known to those skilled in the art, before being reacted with the -(C_1-C_{10})alkyl halide. Suitable protecting groups include, but are not limited to, those described above.

The Hydroxyiminopiperazine Compounds wherein R_4 is -C(O)R_9 can be obtained by reacting a Hydroxyiminopiperaxine Compound wherein R_4 is -H with an acid halide of formula X-C(O)R_9, wherein X and R_9 are defined above, to provide the Hydroxyiminopiperaxine Compound wherein R_4 is -C(O)R_9 as shown below in Scheme **D**.



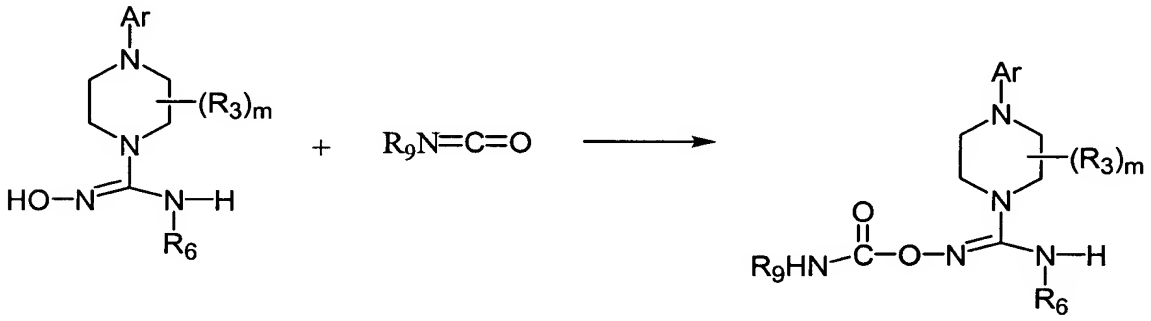
Scheme D

wherein X is -Cl, -Br, -I, or -F and Ar, R_3, R_6, R_9, and m are defined above. If the Ar group of the Hydroxyiminopiperazine Compound wherein R_4 is -H is substituted with a hydroxyl or amino group or -R_3 is a hydroxyl or amino group, the hydroxyl or amino group is protected using a suitable protecting group, using methods well known to those skilled in the art, before being reacted with the acid halide of formula X-C(O)R_9. Suitable protecting groups include, but are not limited to, those described above.

A representative procedure for coupling an acid chloride with an amine is provided in T.R. Herrin *et al., J. Med. Chem.* 1216-1223 (1975). Methods for preparing acid halides are well known to those skilled in the art and are described in J. March, *Advanced Organic Chemistry, Reaction Mechanisms and Structure* 437-8 (4th ed. 1992). For example, acid halides can be prepared by reacting the carboxylic acid with thionyl

chloride, bromide, or iodide. An acid chloride can also be prepared by reacting a carboxylic acid with phosphorous trichloride or tribromide. An acid chloride can also be prepared by reacting the carboxylic acid with Ph_3P in carbon tetrachloride. An acid fluoride can be obtained by reacting a carboxylic acid with cyanuric fluoride.

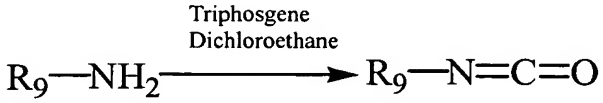
The Hydroxyiminopiperazine Compounds wherein R_4 is $-C(O)NHR_9$ can be obtained by reacting a Hydroxyiminopiperaxine Compound wherein R_4 is -H with an isocyanate, R_9-N=C=O, in a suitable solvent, fore example toluene, at a suitable temperature, for example at reflux temperature, to provide the Hydroxyiminopiperaxine Compound wherein R_4 is $-C(O)NHR_9$ as shown below in Scheme **E**:



Scheme E

wherein Ar, R_3, R_6, R_9, and m are defined above. If the Ar group of the Hydroxyiminopiperazine Compound wherein R_4 is -H is substituted with a hydroxyl or amino group or $-R_3$ is a hydroxyl or amino group, the hydroxyl or amino group is protected using a suitable protecting group, using methods well known to those skilled in the art, before being reacted with the isocyanate of formula R_9-N=C=O. Suitable protecting groups include, but are not limited to, those described above.

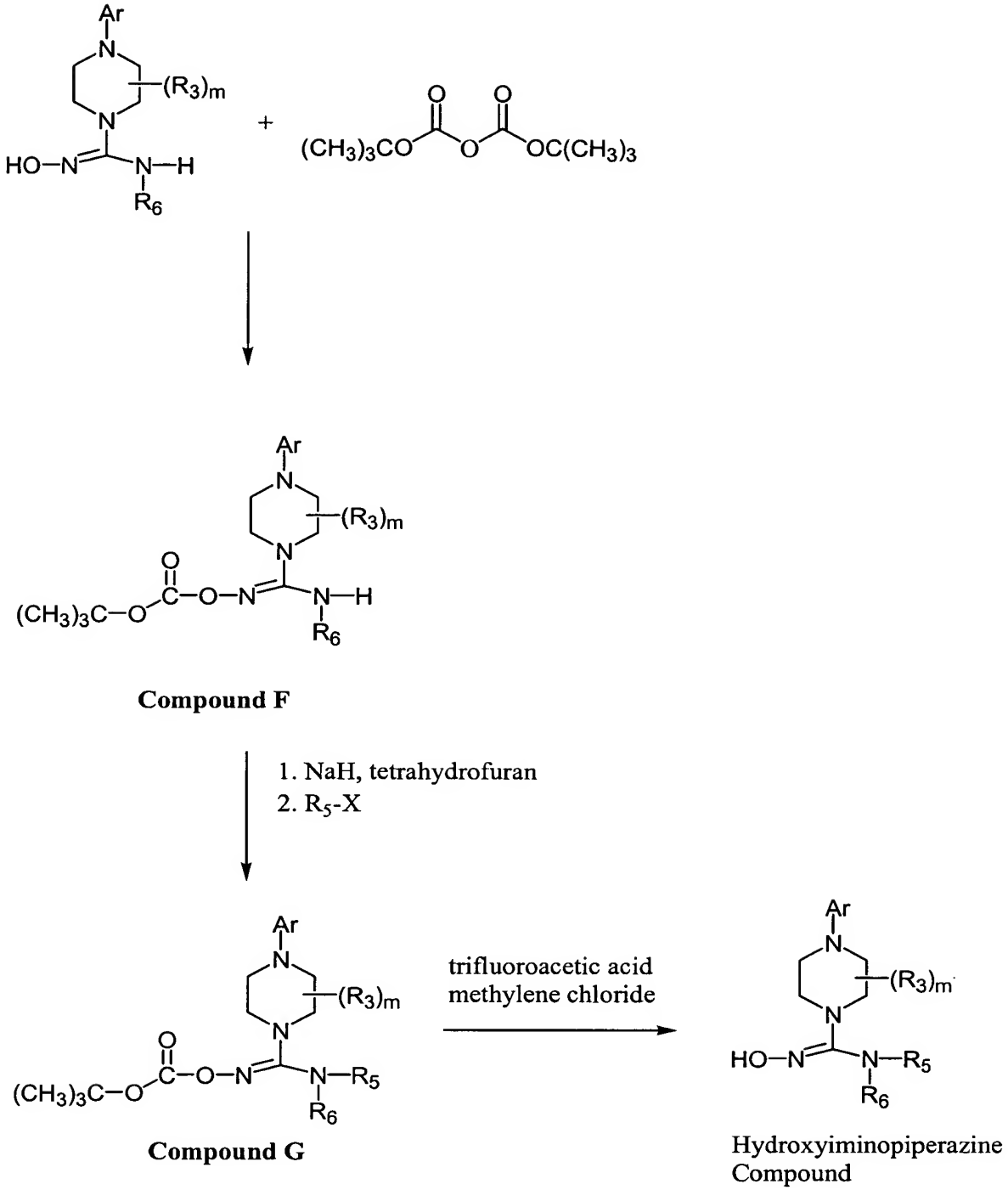
Isocyanates R_9-N=C=O are commercially available or preparable by reacting R_9NH_2 with phosgene according to well-known methods (*See, e.g.*, H. Eckert et al., *Angew. Chem. Int. Ed. Engl.* 26:894 (1987); H. Eckert, Ger. Offen. DE 3 440 141; *Chem Abstr.* 106:4294d (1987); and L. Contarca et al., *Synthesis* 553-576 (1996)). For example an amine, R_9-NH_2, can be reacted with triphosgene in dichloromethane as depicted below in Scheme **F**.



Scheme F

Typically, a solution of triphosgene (0.3 equivalents) in 1,2-dichloroethane (0.3 M) is slowly added to a stirred solution of R_9NH_2 (1.0 equivalents) in 1, 2-dichloroethane (0.3 M) at room temperature. The reaction mixture is then stirred at room temperature for about 10 min. and the temperature then raised to about 70 °C. After stirring at about 70 °C for about 3 h, the reaction mixture is cooled to room temperature, filtered, and the filtrate concentrated to give the desired isocyanate.

The Hydroxyiminopiperazine Compounds wherein R_5 is -(C_1-C_{10})alkyl can be obtained as shown below in Scheme **G**:



Compound F

Compound G

Hydroxyiminopiperazine Compound

Scheme G

wherein Ar, R_3, R_6, and m are defined above; X is -Cl, -Br, -I, or -F; and R_5 -(C_1-C_{10})alkyl.

A Hydroxyiminopiperazine Compound wherein R_4 is -H and R_5 is -H is reacted with di-*tert*-butyldicarbonate in the presence of dimethylaminopyridine in methylene chloride according to well known techniques to provide a compound of formula **F**. The compound of formula **F** is then reacted with sodium hydride in tetrahydrofuran followed by an alkyl halide, R_5-X, wherein R_5 is -(C_1-C_{10})alkyl and X is -Cl, -Br, -I, or -F,

to provide a compound of formula **G**. The compound of formula **G** is then reacted with trifluoroacetic acid in methylene chloride according to well known techniques to provide the Hydroxyiminopiperazine Compound wherein R_5 is -(C_1-C_{10})alkyl.

The Hydroxyiminopiperazine Compounds of formula VI and VII can be obtained by methods analogous to those described above in Scheme **A-G** wherein R_6 of the isothiocyanate, R_6NCS, in Scheme **B** is a phenethyl group or a phenpropyl group.

Certain Hydroxyiminopiperazine Compounds can have one or more asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. A Hydroxyiminopiperazine Compound can be in the form of an optical isomer or a diastereomer. Accordingly, the invention encompasses Hydroxyiminopiperazine Compounds and their uses as described herein in the form of their optical isomers, diasteriomers, and mixtures thereof, including a racemic mixture.

In addition, one or more hydrogen, carbon or other atoms of a Hydroxyiminopiperazine Compound can be replaced by an isotope of the hydrogen, carbon or other atoms. Such compounds, which are encompassed by the present invention, are useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

4.11 Therapeutic Uses of the Hydroxyiminopiperazine Compounds

In accordance with the invention, the Hydroxyiminopiperazine Compounds are administered to an animal in need of treatment or prevention of a Condition.

In one embodiment, an effective amount of a Hydroxyiminopiperazine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting VR1. Examples of conditions that are treatable or preventable by inhibiting VR1 include, but are not limited to, pain, UI, an ulcer, IBD, and IBS.

In another embodiment, an effective amount of a Hydroxyiminopiperazine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting mGluR5. Examples of conditions that are treatable or preventable by inhibiting mGluR5 include, but are not limited to, pain, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, a pruritic condition, and psychosis.

In another embodiment, an effective amount of a Hydroxyiminopiperazine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting mGluR1. Examples of conditions that are treatable or preventable by inhibiting mGluR1 include, but are not limited to, pain, UI, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a

cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, and depression.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent acute or chronic pain. Examples of pain treatable or preventable using the Hydroxyiminopiperazine Compounds include, but are not limited to, cancer pain, central pain, labor pain, myocardial infarction pain, pancreatic pain, colic pain, post-operative pain, headache pain, muscle pain, arthritic pain, and pain associated with a periodontal disease, including gingivitis and periodontitis.

The pain to be treated or prevented may be associated with inflammation associated with an inflammatory disease, which can arise where there is an inflammation of the body tissue, and which can be a local inflammatory response and/or a systemic inflammation. For example, the Phenylene Compounds can be used to treat, or prevent pain associated with inflammatory disease including, but not limited to: organ transplant rejection; reoxygenation injury resulting from organ transplantation (see Grupp *et al.*, *J. Mol, Cell Cardiol.* 31:297-303 (1999)) including, but not limited to, transplantation of the heart, lung, liver, or kidney; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel diseases, such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases, such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye, including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory disease of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory disease of the skin, including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer 's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; autoimmune diseases, including Type I and Type II diabetes mellitus; diabetic complications, including, but not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy (such as microaluminuria and progressive diabetic nephropathy), polyneuropathy, mononeuropathies, autonomic neuropathy, gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, and a

skin or mucous membrane complication (such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabeticorum); immune-complex vasculitis, and systemic lupus erythematosus (SLE); inflammatory disease of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and artherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer. The Phenylene Compounds can also be used for inhibiting, treating, or preventing pain associated with inflammatory disease that can, for example, be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to pro-inflammatory cytokines, *e.g.*, shock associated with pro-inflammatory cytokines. Such shock can be induced, *e.g.*, by a chemotherapeutic agent that is administered as a treatment for cancer.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent UI. Examples of UI treatable or preventable using the Hydroxyiminopiperazine Compounds include, but are not limited to, urge incontinence, stress incontinence, overflow incontinence, neurogenic incontinence, and total incontinence.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent an ulcer. Examples of ulcers treatable or preventable using the Hydroxyiminopiperazine Compounds include, but are not limited to, a duodenal ulcer, a gastric ulcer, a marginal ulcer, an esophageal ulcer, and a stress ulcer.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent IBD, including Crohn's disease and ulcerative colitis.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent IBS. Examples of IBS treatable or preventable using the Hydroxyiminopiperazine Compounds include, but are not limited to, spastic-colon-type IBS and constipation-predominant IBS.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent an addictive disorder, including but not limited to, an eating disorder, an impulse-control disorder, an alcohol-related disorder, a nicotine-related disorder, an amphetamine-related disorder, a cannabis-related disorder, a cocaine-related disorder, an hallucinogen-related disorder, an inhalant-related disorders, and an opioid-related disorder, all of which are further sub-classified as listed below.

Eating disorders include, but are not limited to, Bulimia Nervosa, Nonpurging Type; Bulimia Nervosa, Purging Type; Anorexia; and Eating Disorder not otherwise specified (NOS).

Impulse control disorders include, but are not limited to, Intermittent Explosive Disorder, Kleptomania, Pyromania, Pathological Gambling, Trichotillomania, and Impulse Control Disorder not otherwise specified (NOS).

Alcohol-related disorders include, but are not limited to, Alcohol-Induced Psychotic Disorder with delusions, Alcohol Abuse, Alcohol Intoxication, Alcohol Withdrawal, Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol Dependence, Alcohol-Induced Psychotic Disorder with hallucinations, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder, Alcohol-Related Disorder not otherwise specified (NOS), Alcohol Intoxication, and Alcohol Withdrawal.

Nicotine-related disorders include, but are not limited to, Nicotine Dependence, Nicotine Withdrawal, and Nicotine-Related Disorder not otherwise specified (NOS).

Amphetamine-related disorders include, but are not limited to, Amphetamine Dependence, Amphetamine Abuse, Amphetamine Intoxication, Amphetamine Withdrawal, Amphetamine Intoxication Delirium, Amphetamine-Induced Psychotic Disorder with delusions, Amphetamine-Induced Psychotic Disorders with hallucinations, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder, Amphetamine Related Disorder not otherwise specified (NOS), Amphetamine Intoxication, and Amphetamine Withdrawal.

Cannabis-related disorders include, but are not limited to, Cannabis Dependence, Cannabis Abuse, Cannabis Intoxication, Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder with delusions, Cannabis-Induced Psychotic Disorder with hallucinations, Cannabis-Induced Anxiety Disorder, Cannabis Related Disorder not otherwise specified (NOS), and Cannabis Intoxication.

Cocaine-related disorders include, but are not limited to, Cocaine Dependence, Cocaine Abuse, Cocaine Intoxication, Cocaine Withdrawal, Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder with delusions, Cocaine-Induced Psychotic Disorders with hallucinations, Cocaine-Induced Mood Disorder,

Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder, Cocaine Related Disorder not otherwise specified (NOS), Cocaine Intoxication, and Cocaine Withdrawal.

Hallucinogen-related disorders include, but are not limited to, Hallucinogen Dependence, Hallucinogen Abuse, Hallucinogen Intoxication, Hallucinogen Withdrawal, Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder with delusions, Hallucinogen-Induced Psychotic Disorders with hallucinations, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder, Hallucinogen-Induced Sexual Dysfunction, Hallucinogen-Induced Sleep Disorder, Hallucinogen Related Disorder not otherwise specified (NOS), Hallucinogen Intoxication, and Hallucinogen Persisting Perception Disorder (Flashbacks).

Inhalant-related disorders include, but are not limited to, Inhalant Dependence, Inhalant Abuse, Inhalant Intoxication, Inhalant Intoxication Delirium, Inhalant-Induced Psychotic Disorder with delusions, Inhalant-Induced Psychotic Disorder with hallucinations, Inhalant-Induced Anxiety Disorder, Inhalant Related Disorder not otherwise specified (NOS), and Inhalant Intoxication.

Opioid-related disorders include, but are not limited to, Opioid Dependence, Opioid Abuse, Opioid Intoxication, Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder with delusions, Opioid-Induced Psychotic Disorder with hallucinations, Opioid-Induced Anxiety Disorder, Opioid Related Disorder not otherwise specified (NOS), Opioid Intoxication, and Opioid Withdrawal.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent Parkinson's disease and parkinsonism and the symptoms associated with Parkinson's disease and parkinsonism, including but not limited to, bradykinesia, muscular rigidity, resting tremor, and impairment of postural balance.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent generalized anxiety or severe anxiety and the symptoms associated with anxiety, including but not limited to, restlessness; tension; tachycardia; dyspnea; depression, including chronic "neurotic" depression; panic disorder; agoraphobia and other specific phobias; eating disorders; and personality disorders.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent epilepsy, including but not limited to, partial epilepsy, generalized epilepsy, and the symptoms associated with epilepsy, including but not limited to, simple partial seizures,

jacksonian seizures, complex partial (psychomotor) seizures, convulsive seizures (grand mal or tonic-clonic seizures), petit mal (absence) seizures, and status epilepticus.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent strokes, including but not limited to, ischemic strokes and hemorrhagic strokes.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent a seizure, including but not limited to, infantile spasms, febrile seizures, and epileptic seizures.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent a pruritic condition, including but not limited to, pruritus caused by dry skin, scabies, dermatitis, herpetiformis, atopic dermatitis, *pruritus vulvae et ani*, miliaria, insect bites, pediculosis, contact dermatitis, drug reactions, urticaria, urticarial eruptions of pregnancy, psoriasis, lichen planus, lichen simplex chronicus, exfoliative dermatitis, folliculitis, bullous pemphigoid, or fiberglass dermatitis.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent psychosis, including but not limited to, schizophrenia, including paranoid schizophrenia, hebephrenic or disorganized schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, negative or deficit subtype schizophrenia, and non-deficit schizophrenia; a delusional disorder, including erotomanic subtype delusional disorder, grandiose subtype delusional disorder, jealous subtype delusional disorder, persecutory subtype delusional disorder, and somatic subtype delusional disorder; and brief psychosis.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent a cognitive disorder, including but not limited to, delirium and dementia such as multi-infarct dementia, dementia pugilistica, dimentia caused by AIDS, and dementia caused by Alzheimer's disease.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent a memory deficiency, including but not limited to, dissociative amnesia and dissociative fugue.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent restricted brain function, including but not limited to, that caused by surgery or an organ transplant, restricted blood supply to the brain, a spinal cord injury, a head injury, hypoxia, cardiac arrest, or hypoglycemia.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent Huntington's chorea.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent ALS.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent retinopathy, including but not limited to, arteriosclerotic retinopathy, diabetic arteriosclerotic retinopathy, hypertensive retinopathy, non-proliferative retinopathy, and proliferative retinopathy. The Hydroxyiminopiperazine Compounds can be used to treat or prevent a muscle spasm.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent a migraine including, but not limited to, migraine without aura ("common migraine"), migraine with aura ("classic migraine"), migraine without headache, basilar migraine, familial hemiplegic migraine, migrainous infarction, and migraine with prolonged aura.

The Hydroxyiminopiperazine Compounds can be used to treat or vomiting, including but not limited to, nausea vomiting, dry vomiting (retching), and regurgitation.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent dyskinesia, including but not limited to, tardive dyskinesia and biliary dyskinesia.

The Hydroxyiminopiperazine Compounds can be used to treat or prevent depression, including but not limited to, major depression and bipolar disorder.

Without wishing to be bound by theory, Applicants believe that the Hydroxyiminopiperazine Compounds are antagonists for VR1.

The invention also relates to methods for inhibiting VR1 function in a cell, comprising contacting a cell capable of expressing VR1 with an amount of a Hydroxyiminopiperazine Compound effective to inhibit VR1 function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express VR1 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, UI, an ulcer, IBD, or IBS. The method is also useful for inhibiting VR1 function in a cell *in vivo*, in an animal (*e.g.*, a human), by contacting a cell in an animal with an effective amount of a Hydroxyiminopiperazine Compound. In one embodiment, the method is useful for treating or preventing pain in an animal in need thereof. In another embodiment, the method is useful for treating or preventing UI in an animal in need thereof. In another embodiment, the method is useful for treating or preventing an ulcer in an animal in need thereof. In another embodiment, the method is useful for treating or preventing IBD in an animal in need thereof. In another embodiment, the method is useful for treating or preventing IBS in an animal in need thereof.

Examples of tissue comprising cells capable of expressing VR1 include, but are not limited to, neuronal, brain, kidney, urothelium, and bladder tissue. Methods for assaying cells that express VR1 are well known in the art.

Without wishing to be bound by theory, Applicants believe that the Hydroxyiminopiperazine Compounds are antagonists for mGluR5.

The invention further relates to methods for inhibiting mGluR5 function in a cell, comprising contacting a cell capable of expressing mGluR5 with an amount of a Hydroxyiminopiperazine Compound effective to inhibit mGluR5 function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express mGluR5 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, a pruritic condition, or psychosis. The method is also useful for inhibiting mGluR5 function in a cell *in vivo*, in an animal (*e.g.*, a human), by contacting a cell in an animal with an amount of a Hydroxyiminopiperazine Compound effective to inhibit mGluR5 function in the cell. In one embodiment, the method is useful for treating or preventing pain in an animal in need thereof. In another embodiment, the method is useful for treating or preventing an addictive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Parkinson's disease in an animal in need thereof. In another embodiment, the method is useful for treating or preventing parkinsonism in an animal in need thereof. In another embodiment, the method is useful for treating or preventing anxiety in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a pruritic condition in an animal in need thereof. In another embodiment, the method is useful for treating or preventing psychosis in an animal in need thereof.

Examples of cells capable of expressing mGluR5 are neuronal and glial cells of the central nervous system, particularly the brain, especially in the nucleus accumbens. Methods for assaying cells that express mGluR5 are well known in the art.

Without wishing to be bound by theory, Applicants believe that the Hydroxyiminopiperazine Compounds are antagonists for mGluR1.

The invention further relates to methods for inhibiting mGluR1 function in a cell, comprising contacting a cell capable of expressing mGluR1 with an amount of a Hydroxyiminopiperazine Compound effective to inhibit mGluR1 function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express mGluR1 and, accordingly, are useful as part of an assay to select compounds useful for treating or

preventing pain, UI, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression. The method is also useful for inhibiting mGluR1 function in a cell *in vivo*, in an animal (*e.g.*, a human), by contacting a cell in an animal with an amount of a Hydroxyiminopiperazine Compound effective to inhibit mGluR1 function in the cell. In one embodiment, the method is useful for treating or preventing pain in an animal in need thereof. In another embodiment, the method is useful for treating or preventing UI in an animal in need thereof. In another embodiment, the method is useful for treating or preventing an addictive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Parkinson's disease in an animal in need thereof. In another embodiment, the method is useful for treating or preventing parkinsonism in an animal in need thereof. In another embodiment, the method is useful for treating or preventing anxiety in an animal in need thereof. In another embodiment, the method is useful for treating or preventing epilepsy in an animal in need thereof. In another embodiment, the method is useful for treating or preventing stroke in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a seizure in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a pruritic condition in an animal in need thereof. In another embodiment, the method is useful for treating or preventing psychosis in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a cognitive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a memory deficit in an animal in need thereof. In another embodiment, the method is useful for treating or preventing restricted brain function in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Huntington's chorea in an animal in need thereof. In another embodiment, the method is useful for treating or preventing ALS in an animal in need thereof. In another embodiment, the method is useful for treating or preventing dementia in an animal in need thereof. In another embodiment, the method is useful for treating or preventing retinopathy in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a muscle spasm in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a migraine in an animal in need thereof. In another embodiment, the method is useful for treating, preventing, or inhibiting vomiting in an animal in need thereof. In another embodiment, the method is useful for treating or

preventing dyskinesia in an animal in need thereof. In another embodiment, the method is useful for treating or preventing depression in an animal in need thereof.

Examples of cells capable of expressing mGluR1 include, but are not limited to, cerebellar Purkinje neuron cells, Purkinje cell bodies (punctate), cells of spine(s) of the cerebellum; neurons and neurophil cells of olfactory-bulb glomeruli; cells of the superficial layer of the cerebral cortex; hippocampus cells; thalamus cells; superior colliculus cells; and spinal trigeminal nucleus cells. Methods for assaying cells that express MGluR1 are well known in the art.

4.11.1 THERAPEUTIC/PROPHYLACTIC ADMINISTRATION AND COMPOSITIONS OF THE INVENTION

Due to their activity, the Hydroxyiminopiperazine Compounds are advantageously useful in veterinary and human medicine. As described above, the Hydroxyiminopiperazine Compounds are useful for treating or preventing a Condition in an animal in need thereof.

When administered to an animal, the Hydroxyiminopiperazine Compounds are administered as a component of a composition that comprises a pharmaceutically acceptable carrier or excipient. The present compositions, which comprise a Hydroxyiminopiperazine Compound, can be administered orally. The Hydroxyiminopiperazine Compounds of the invention can also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral, rectal, and intestinal mucosa, *etc.*) and can be administered together with another biologically active agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.*, and can be used to administer the Hydroxyiminopiperazine Compound.

Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the practitioner. In most instances, administration will result in the release of the Hydroxyiminopiperazine Compounds into the bloodstream.

In specific embodiments, it can be desirable to administer the Hydroxyiminopiperazine Compounds locally. This can be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in

conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, it can be desirable to introduce the Hydroxyiminopiperazine Compounds into the central nervous system or gastrointestinal tract by any suitable route, including intraventricular, intrathecal, and epidural injection, and enema. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, the Hydroxyiminopiperazine Compounds can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

In another embodiment, the Hydroxyiminopiperazine Compounds can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science* 249:1527-1533 (1990) and Treat *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989).

In yet another embodiment, the Hydroxyiminopiperazine Compounds can be delivered in a controlled-release system or sustained-release system (*see, e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled- or sustained-release systems discussed in the review by Langer, *Science* 249:1527-1533 (1990) can be used. In one embodiment, a pump can be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); and Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (*see Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); Levy *et al.*, *Science* 228:190 (1985); During *et al.*, *Ann. Neurol.* 25:351 (1989); and Howard *et al.*, *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled- or sustained-release system can be placed in proximity of a target of the Hydroxyiminopiperazine Compounds, *e.g.*, the spinal column, brain, or gastrointestinal tract, thus requiring only a fraction of the systemic dose.

The present compositions can optionally comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration to the animal. Such a pharmaceutical excipient can be a liquid, such as water or an oil, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical excipient can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipient is sterile when administered to an animal. Water is a particularly useful excipient when the Hydroxyiminopiperazine Compound is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The present compositions can take the form of solutions, suspensions, emulsions, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule (see *e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995), incorporated herein by reference.

In one embodiment, the Hydroxyiminopiperazine Compounds are formulated in accordance with routine procedures as a composition adapted for oral administration to human beings. Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also

suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.

In another embodiment, the Hydroxyiminopiperazine Compounds can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lignocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the Hydroxyiminopiperazine Compounds are to be administered by infusion, they can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the Hydroxyiminopiperazine Compounds are administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

The Hydroxyiminopiperazine Compounds can be administered by controlled-release or sustained-release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration

such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

Controlled- or sustained-release pharmaceutical compositions can have a common goal of improving drug therapy over that achieved by their non-controlled or non-sustained-release counterparts. In one embodiment, a controlled- or sustained-release composition comprises a minimal amount of a Hydroxyiminopiperazine Compound to treat or prevent the Condition in a minimum amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Hydroxyiminopiperazine Compound, and can thus reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially release an amount of a Hydroxyiminopiperazine Compound that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Hydroxyiminopiperazine Compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the Hydroxyiminopiperazine Compound in the body, the Hydroxyiminopiperazine Compound can be released from the dosage form at a rate that will replace the amount of Hydroxyiminopiperazine Compound being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

The amount of the Hydroxyiminopiperazine Compound that is effective for the treatment or prevention of a Condition can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on the route of administration, and the seriousness of the Condition and can be decided according to the judgment of a practitioner and/or each animal's circumstances. Suitable effective dosage amounts, however, range from about 0.01 mg/kg of body weight to about 2500 mg/kg of body weight, although they are typically about 100 mg/kg of body weight or less. In one embodiment, the effective dosage amount ranges from about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a Hydroxyiminopiperazine Compound,

in another embodiment, about 0.020 mg/kg of body weight to about 50 mg/kg of body weight, and in another embodiment, about 0.025 mg/kg of body weight to about 20 mg/kg of body weight. In one embodiment, an effective dosage amount is administered about every 24 h until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 12 h until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 8 h until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 6 h until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 4 h until the Condition is abated. The effective dosage amounts described herein refer to total amounts administered; that is, if more than one Hydroxyiminopiperazine Compound is administered, the effective dosage amounts correspond to the total amount administered.

Where a cell capable of expressing VR1, mGluR5, or mGluR1 is contacted with a Hydroxyiminopiperazine Compound *in vitro*, the amount effective for inhibiting the VR1, mGluR5, or mGluR1 receptor function in a cell will typically range from about 0.01 μg/L to about 5 mg/L, in one embodiment, from about 0.01 μg/L to about 2.5 mg/L, in another embodiment, from about 0.01 μg/L to about 0.5 mg/L, and in another embodiment, from about 0.01 μg/L to about 0.25 mg/L of a solution or suspension of a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Hydroxyiminopiperazine Compound is from about 0.01 μL to about 1 mL. In another embodiment, the volume of solution or suspension is about 200 μL.

Where a cell capable of expressing VR1, mGluR5, or mGluR1 is contacted with a Hydroxyiminopiperazine Compound *in vivo*, the amount effective for inhibiting the receptor function in a cell will typically range from about 0.01 mg/kg of body weight to about 2500 mg/kg of body weight, although it typically ranges from about 100 mg/kg of body weight or less. In one embodiment, the effective dosage amount ranges from about 0.01 mg/kg of body weight to about 100 mg/kg of body weight of a Hydroxyiminopiperazine Compound, in another embodiment, about 0.02 mg/kg of body weight to about 50 mg/kg of body weight, and in another embodiment, about 0.025 mg/kg of body weight to about 20 mg/kg of body weight. In one embodiment, an effective dosage amount is administered about every 24 h. In another embodiment, an effective dosage amount is administered about every 12. In another embodiment, an effective dosage amount is administered about every 8. In another embodiment, an effective dosage amount

is administered about every 6 h. In another embodiment, an effective dosage amount is administered about every 4 h.

The Hydroxyiminopiperazine Compounds can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

The present methods for treating or preventing a Condition in an animal in need thereof can further comprise administering to the animal being administered a Hydroxyiminopiperazine Compound another therapeutic agent. In one embodiment, the other therapeutic agent is administered in an effective amount.

The present methods for inhibiting VR1 function in a cell capable of expressing VR1 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The present methods for inhibiting mGluR5 function in a cell capable of expressing mGluR5 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The present methods for inhibiting mGluR1 function in a cell capable of expressing mGluR1 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The other therapeutic agent includes, but is not limited to, an opioid agonist, a non-opioid analgesic, a non-steroid anti-inflammatory agent, an antimigraine agent, a Cox-II inhibitor, an antiemetic, a β-adrenergic blocker, an anticonvulsant, an antidepressant, a Ca2+-channel blocker, an anticancer agent, an agent for treating or preventing UI, an agent for treating or preventing an ulcer, an agent for treating or preventing IBD, an agent for treating or preventing IBS, an agent for treating addictive disorder, an agent for treating Parkinson's disease and parkinsonism, an agent for treating anxiety, an agent for treating epilepsy, an agent for treating a stroke, an agent for treating a seizure, an agent for treating a pruritic condition, an agent for treating psychosis, an agent for treating Huntington's chorea, an agent for treating ALS, an agent for treating a cognitive disorder, an agent for treating a migraine, an agent for treating or inhibiting vomiting, an agent for treating dyskinesia, or an agent for treating depression, and mixtures thereof.

Effective amounts of the other therapeutic agents are well known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective-amount range. In one embodiment of the invention, where another therapeutic agent is administered to an animal, the effective

amount of the Hydroxyiminopiperazine Compound is less than its effective amount would be where the other therapeutic agent is not administered. In this case, without being bound by theory, it is believed that the Hydroxyiminopiperazine Compounds and the other therapeutic agent act synergistically to treat or prevent a Condition.

Examples of useful opioid agonists include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

In certain embodiments, the opioid agonist is selected from codeine, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphine, morphine, tramadol, oxymorphone, pharmaceutically acceptable salts thereof, and mixtures thereof.

Examples of useful non-opioid analgesics include non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, and pharmaceutically acceptable salts thereof, and mixtures thereof. Other suitable non-opioid analgesics include the following, non-limiting, chemical classes of analgesic, antipyretic, nonsteroidal anti-inflammatory drugs: salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophennol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin,

sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone. For a more detailed description of the NSAIDs, *see Paul A. Insel, Analgesic-Antipyretic and Anti-inflammatory Agents and Drugs Employed in the Treatment of Gout, in Goodman & Gilman's The Pharmacological Basis of Therapeutics* 617-57 (Perry B. Molinhoff and Raymond W. Ruddon eds., 9th ed 1996) and Glen R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II* 1196-1221 (A.R. Gennaro ed. 19th ed. 1995) which are hereby incorporated by reference in their entireties.

Examples of useful Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof, are described in U.S. Patent No. 6,136,839, which is hereby incorporated by reference in its entirety. Examples of useful Cox-II inhibitors include, but are not limited to, rofecoxib and celecoxib.

Examples of useful antimigraine agents include, but are not limited to, alpiropride, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergot, ergotamine, flumedroxone acetate, fonazine, lisuride, lomerizine, methysergide oxetorone, pizotyline, and mixtures thereof.

The other therapeutic agent can also be an antiemetic agent. Examples of useful antiemetic agents include, but are not limited to, metoclopromide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and mixtures thereof.

Examples of useful β-adrenergic blockers include, but are not limited to, acebutolol, alprenolol, amosulabol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butidrine hydrochloride, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, esmolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nifenalol, nipradilol, oxprenolol,

penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, and xibenolol.

Examples of useful anticonvulsants include, but are not limited to, acetylpheneturide, albutoin, aloxidone, aminoglutethimide, 4-amino-3-hydroxybutyric acid, atrolactamide, beclamide, buramate, calcium bromide, carbamazepine, cinromide, clomethiazole, clonazepam, decimemide, diethadione, dimethadione, doxenitroin, eterobarb, ethadione, ethosuximide, ethotoin, felbamate, fluoresone, gabapentin, 5-hydroxytryptophan, lamotrigine, magnesium bromide, magnesium sulfate, mephenytoin, mephobarbital, metharbital, methetoin, methsuximide, 5-methyl-5-(3-phenanthryl)-hydantoin, 3-methyl-5-phenylhydantoin, narcobarbital, nimetazepam, nitrazepam, oxcarbazepine, paramethadione, phenacemide, phenetharbital, pheneturide, phenobarbital, phensuximide, phenylmethylbarbituric acid, phenytoin, phethenylate sodium, potassium bromide, pregabaline, primidone, progabide, sodium bromide, solanum, strontium bromide, suclofenide, sulthiame, tetrantoin, tiagabine, topiramate, trimethadione, valproic acid, valpromide, vigabatrin, and zonisamide.

Examples of useful antidepressants include, but are not limited to, binedaline, caroxazone, citalopram, (S)-citalopram, dimethazan, fencamine, indalpine, indeloxazine hydrocholoride, nefopam, nomifensine, oxitriptan, oxypertine, paroxetine, sertraline, thiazesim, trazodone, benmoxine, iproclozide, iproniazid, isocarboxazid, nialamide, octamoxin, phenelzine, cotinine, rolicyprine, rolipram, maprotiline, metralindole, mianserin, mirtazepine, adinazolam, amitriptyline, amitriptylinoxide, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, nortriptyline, noxiptilin, opipramol, pizotyline, propizepine, protriptyline, quinupramine, tianeptine, trimipramine, adrafinil, benactyzine, bupropion, butacetin, dioxadrol, duloxetine, etoperidone, febarbamate, femoxetine, fenpentadiol, fluoxetine, fluvoxamine, hematoporphyrin, hypericin, levophacetoperane, medifoxamine, milnacipran, minaprine, moclobemide, nefazodone, oxaflozane, piberaline, prolintane, pyrisuccideanol, ritanserin, roxindole, rubidium chloride, sulpiride, tandospirone, thozalinone, tofenacin, toloxatone, tranylcypromine, L-tryptophan, venlafaxine, viloxazine, and zimeldine.

Examples of useful Ca2+-channel blockers include, but are not limited to, bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine,

nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, fantofarone, and perhexiline.

Examples of useful anticancer agents include, but are not limited to, acivicin, aclarubicin, acodazole hydrochloride, acronine, adozelesin, aldesleukin, altretamine, ambomycin, ametantrone acetate, aminoglutethimide, amsacrine, anastrozole, anthramycin, asparaginase, asperlin, azacitidine, azetepa, azotomycin, batimastat, benzodepa, bicalutamide, bisantrene hydrochloride, bisnafide dimesylate, bizelesin, bleomycin sulfate, brequinar sodium, bropirimine, busulfan, cactinomycin, calusterone, caracemide, carbetimer, carboplatin, carmustine, carubicin hydrochloride, carzelesin, cedefingol, chlorambucil, cirolemycin, cisplatin, cladribine, crisnatol mesylate, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin hydrochloride, decitabine, dexormaplatin, dezaguanine, dezaguanine mesylate, diaziquone, docetaxel, doxorubicin, doxorubicin hydrochloride, droloxifene, droloxifene citrate, dromostanolone propionate, duazomycin, edatrexate, eflornithine hydrochloride, elsamitrucin, enloplatin, enpromate, epipropidine, epirubicin hydrochloride, erbulozole, esorubicin hydrochloride, estramustine, estramustine phosphate sodium, etanidazole, etoposide, etoposide phosphate, etoprine, fadrozole hydrochloride, fazarabine, fenretinide, floxuridine, fludarabine phosphate, fluorouracil, flurocitabine, fosquidone, fostriecin sodium, gemcitabine, gemcitabine hydrochloride, hydroxyurea, idarubicin hydrochloride, ifosfamide, ilmofosine, interleukin II (including recombinant interleukin II or rIL2), interferon alfa-2a, interferon alfa-2b, interferon alfa-n1 , interferon alfa-n3, interferon beta-I a, interferon gamma-I b, iproplatin, irinotecan hydrochloride, lanreotide acetate, letrozole, leuprolide acetate, liarozole hydrochloride, lometrexol sodium, lomustine, losoxantrone hydrochloride, masoprocol, maytansine, mechlorethamine hydrochloride, megestrol acetate, melengestrol acetate, melphalan, menogaril, mercaptopurine, methotrexate, methotrexate sodium, metoprine, meturedepa, mitindomide, mitocarcin, mitocromin, mitogillin, mitomalcin, mitomycin, mitosper, mitotane, mitoxantrone hydrochloride, mycophenolic acid, nocodazole, nogalamycin, ormaplatin, oxisuran, paclitaxel, pegaspargase, peliomycin, pentamustine, peplomycin sulfate, perfosfamide, pipobroman, piposulfan, piroxantrone hydrochloride, plicamycin, plomestane, porfimer sodium, porfiromycin, prednimustine, procarbazine hydrochloride, puromycin, puromycin hydrochloride, pyrazofurin, riboprine, rogletimide, safingol, safingol hydrochloride, semustine, simtrazene, sparfosate sodium, sparsomycin, spirogermanium hydrochloride, spiromustine, spiroplatin, streptonigrin, streptozocin, sulofenur, talisomycin, tecogalan sodium, tegafur, teloxantrone hydrochloride, temoporfin,

teniposide, teroxirone, testolactone, thiamiprine, thioguanine, thiotepa, tiazofurin, tirapazamine, toremifene citrate, trestolone acetate, triciribine phosphate, trimetrexate, trimetrexate glucuronate, triptorelin, tubulozole hydrochloride, uracil mustard, uredepa, vapreotide, verteporfin, vinblastine sulfate, vincristine sulfate, vindesine, vindesine sulfate, vinepidine sulfate, vinglycinate sulfate, vinleurosine sulfate, vinorelbine tartrate, vinrosidine sulfate, vinzolidine sulfate, vorozole, zeniplatin, zinostatin, zorubicin hydrochloride.

Examples of other anti-cancer drugs include, but are not limited to, 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone;

fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator;

protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

Examples of useful therapeutic agents for treating or preventing UI include, but are not limited to, propantheline, imipramine, hyoscyamine, oxybutynin, and dicyclomine.

Examples of useful therapeutic agents for treating or preventing an ulcer include, antacids such as aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, and calcium bicarbonate; sucraflate; bismuth compounds such as bismuth subsalicylate and bismuth subcitrate; H_2 antagonists such as cimetidine, ranitidine, famotidine, and nizatidine; H^+, K^+ - ATPase inhibitors such as omeprazole, iansoprazole, and lansoprazole;

carbenoxolone; misprostol; and antibiotics such as tetracycline, metronidazole, timidazole, clarithromycin, and amoxicillin.

Examples of useful therapeutic agents for treating or preventing IBD include, but are not limited to, anticholinergic drugs; diphenoxylate; loperamide; deodorized opium tincture; codeine; broad-spectrum antibiotics such as metronidazole; sulfasalazine; olsalazie; mesalamine; prednisone; azathioprine; mercaptopurine; and methotrexate.

Examples of useful therapeutic agents for treating or preventing IBS include, but are not limited to, propantheline; muscarine receptor antogonists such as pirenzapine, methoctramine, ipratropium, tiotropium, scopolamine, methscopolamine, homatropine, homatropine methylbromide, and methantheline; and antidiarrheal drugs such as diphenoxylate and loperamide.

Examples of useful therapeutic agents for treating or preventing an addictive disorder include, but are not limited to, methadone, desipramine, amantadine, fluoxetine, buprenorphine, an opiate agonist, 3-phenoxypyridine, levomethadyl acetate hydrochloride, and serotonin antagonists.

Examples of useful therapeutic agents for treating or preventing Parkinson's disease and parkinsonism include, but are not limited to, carbidopa/levodopa, pergolide, bromocriptine, ropinirole, pramipexole, entacapone, tolcapone, selegiline, amantadine, and trihexyphenidyl hydrochloride.

Examples of useful therapeutic agents for treating or preventing anxiety include, but are not limited to, benzodiazepines, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, and triazolam; non-benzodiazepine agents, such as buspirone, gepirone, ipsaprione, tiospirone, zolpicone, zolpidem, and zaleplon; tranquilizers, such as barbituates, *e.g.*, amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, and thiopental; and propanediol carbamates, such as meprobamate and tybamate.

Examples of useful therapeutic agents for treating or preventing epilepsy include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrignine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, bemzodiaepines, gabapentin, lamotrigine, γ-vinyl GABA, acetazolamide, and felbamate.

Examples of useful therapeutic agents for treating or preventing stroke include, but are not limited to, anticoagulants such as heparin, agents that break up clots

such as streptokinase or tissue plasminogen activator, agents that reduce swelling such as mannitol or corticosteroids, and acetylsalicylic acid.

Examples of useful therapeutic agents for treating or preventing a seizure include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrignine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, bemzodiaepines, gabapentin, lamotrigine, γ-vinyl GABA, acetazolamide, and felbamate.

Examples of useful therapeutic agents for treating or preventing a pruritic condition include, but are not limited to, naltrexone; nalmefene; danazol; tricyclics such as amitriptyline, imipramine, and doxepin; antidepressants such as those given below, menthol; camphor; phenol; pramoxine; capsaicin; tar; steroids; and antihistamines.

Examples of useful therapeutic agents for treating or preventing psychosis include, but are not limited to, phenothiazines such as chlorpromazine hydrochloride, mesoridazine besylate, and thoridazine hydrochloride; thioxanthenes such as chloroprothixene and thiothixene hydrochloride; clozapine; risperidone; olanzapine; quetiapine; quetiapine fumarate; haloperidol; haloperidol decanoate; loxapine succinate; molindone hydrochloride; pimozide; and ziprasidone.

Examples of useful therapeutic agents for treating or preventing Huntington's chorea include, but are not limited to, haloperidol and pimozide.

Examples of useful therapeutic agents for treating or preventing ALS include, but are not limited to, baclofen, neurotrophic factors, riluzole, tizanidine, benzodiazepines such as clonazepan and dantrolene.

Examples of useful therapeutic agents for treating or preventing cognitive disorders include, but are not limited to, agents for treating or preventing dementia such as tacrine; donepezil; ibuprofen; antipsychotic drugs such as thioridazine and haloperidol; and antidepressant drugs such as those given below.

Examples of useful therapeutic agents for treating or preventing a migraine include, but are not limited to, sumatriptan; methysergide; ergotamine; caffeine; and beta-blockers such as propranolol, verapamil, and divalproex.

Examples of useful therapeutic agents for treating, preventing, or inhibiting vomiting include, but are not limited to, 5-HT_3 receptor antagonists such as ondansetron, dolasetron, granisetron, and tropisetron; dopamine receptor antagonists such as prochlorperazine, thiethylperazine, chlorpromazin, metoclopramide, and domperidone; glucocorticoids such as dexamethasone; and benzodiazepines such as lorazepam and alprazolam.

Examples of useful therapeutic agents for treating or preventing dyskinesia include, but are not limited to, reserpine and tetrabenazine.

Examples of useful therapeutic agents for treating or preventing depression include, but are not limited to, tricyclic antidepressants such as amitryptyline, amoxapine, bupropion, citalopram, (S)-citalopram, clomipramine, desipramine, doxepin, imipramine, maprotilinr, nefazadone, nortriptyline, protriptyline, trazodone, trimipramine, and venlaflaxine; selective serotonin reuptake inhibitors such as fluoxetine, fluvoxamine, paroxetine, and setraline; monoamine oxidase inhibitors such as isocarboxazid, pargyline, phenelzine, and tranylcypromine; and psychostimulants such as dextroamphetamine and methylphenidate.

A Hydroxyiminopiperazine Compound and the other therapeutic agent can act additively or, in one embodiment, synergistically. In one embodiment, a Hydroxyiminopiperazine Compound is administered concurrently with another therapeutic agent. In one embodiment, a composition comprising an effective amount of a Hydroxyiminopiperazine Compound and an effective amount of another therapeutic agent can be administered. Alternatively, a composition comprising an effective amount of a Hydroxyiminopiperazine Compound and a different composition comprising an effective amount of another therapeutic agent can be concurrently administered. In another embodiment, an effective amount of a Hydroxyiminopiperazine Compound is administered prior or subsequent to administration of an effective amount of another therapeutic agent. In this embodiment, the Hydroxyiminopiperazine Compound is administered while the other therapeutic agent exerts its therapeutic effect, or the other therapeutic agent is administered while the Hydroxyiminopiperazine Compound exerts its preventative or therapeutic effect for treating or preventing a Condition in an animal.

A composition of the invention is prepared by a method comprising admixing a Hydroxyiminopiperazine Compound and a pharmaceutically acceptable carrier or excipient. Admixing can be accomplished using methods well known for admixing a compound (or salt) and a pharmaceutically acceptable carrier or excipient. In one embodiment, the Hydroxyiminopiperazine Compound is present in the composition in an effective amount.

4.11.1 KITS

The invention encompasses kits that can simplify the administration of a Hydroxyiminopiperazine Compound to an animal.

A typical kit of the invention comprises a unit dosage form of a Hydroxyiminopiperazine Compound. In one embodiment, the unit dosage form is a container, which can be sterile, containing an effective amount of a Hydroxyiminopiperazine Compound and a pharmaceutically acceptable carrier or excipient. The kit can further comprise a label or printed instructions instructing the use of the Hydroxyiminopiperazine Compound to treat a Condition. The kit can also further comprise a unit dosage form of another therapeutic agent, for example, a container containing an effective amount of the other therapeutic agent. In one embodiment, the kit comprises a container containing an effective amount of a Hydroxyiminopiperazine Compound and an effective amount of another therapeutic agent. Examples of other therapeutic agents include, but are not limited to, those listed above.

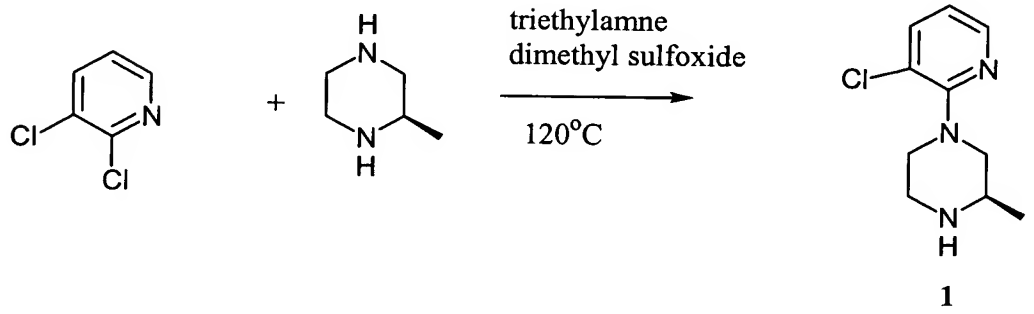
Kits of the invention can further comprise a device that is useful for administering the unit dosage forms. Examples of such a device includes, but are not limited to, a syringe, a drip bag, a patch, an inhaler, and an enema bag.

The following examples are set forth to assist in understanding the invention and should not, of course, be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

5. Examples

Examples 1-10 relate to the synthesis of illustrative Hydroxyiminopiperazine Compounds.

5.1 Example 1: Synthesis of Compound A1(c)



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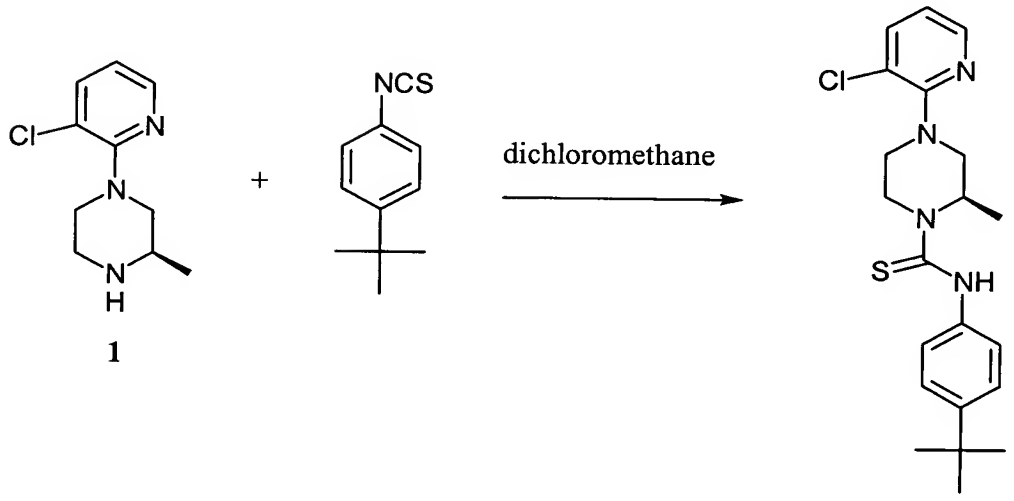

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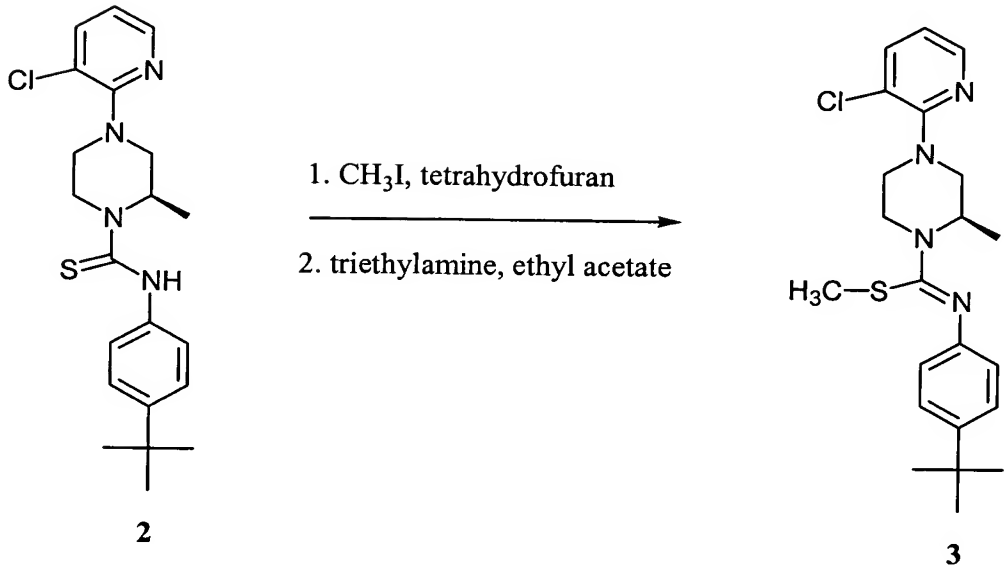

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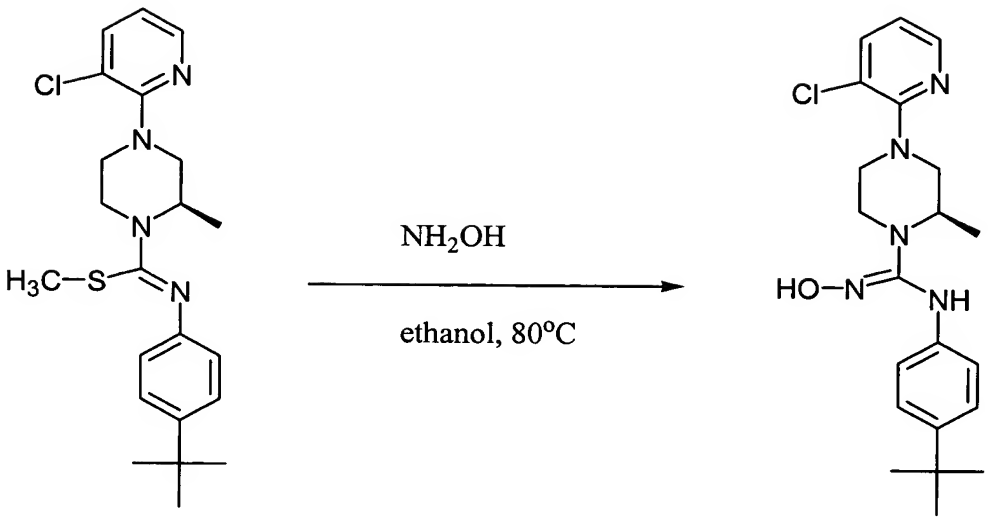

3

Compound A1(c)

2,3-Dichloropyridine (2.94 g, 20.0 mmol), (R)-2-methylpiperazine (2.75 g, 27.5 mmol) (Commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)), and triethylamine (3.04 g, 30 mmol) were dissolved in 15 mL of dimethylsulfoxide and the resulting mixture was heated at about 100°C for about 24 h. The reaction mixture was then cooled to room temperature and extracted with a saturated aqueous sodium bicarbonate solution. The organic layer was dried, concentrated, and purified using a silica gel column eluted with a gradient elution (ethyl acetate to 2:1 ethyl acetate:methanol) to provide Compound **1** (N-(3-chloropyridin-2-yl)-piperazine) as a yellow liquid (90% yield).

A solution of Compound **1** (1.0 mmol) and 4-(*tert*-butyl)-phenylisothiocyanate (commercially available from Ryan Scientific Inc. of Isle of Palms, SC (www.ryansci.com)) (1.0 mmol) in 1.5 mL of dichloromethane was stirred at room temperature (about 25 °C) for about 5 h. The mixture was then concentrated under reduced pressure and directly purified using a silica gel column eluted with a gradient elution (10:1 hexane:ethyl acetate to 3:1 hexane:ethyl acetate) to provide Compound **2** (63% yield). The identity of Compound **2** was confirmed using ^{1}H NMR.

Compound **2**: ^{1}H NMR ($CDCl_3$) δ 8.21(dd, J = 1.6, 4.8 Hz, 1H), 7.63 (dd, J = 1.6, 7.8 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 6.91 (dd, J = 4.8, 7.8 Hz, 1H), 5.14 (br, 1H), 4.41 (dd, J = 13.1 Hz, 1 H), 3.76 (m, 2H), 3.58 (dt, J = 3.4, 12.5 Hz, 1H), 3.17 (dd, J = 3.4, 12.5 Hz, 1H), 3.02 (dt, J = 3.4, 12.5 Hz, 1H), 1.51 (d, J = 6.75 Hz, 3H), 1.33 (s, 9H) ppm.

A solution of Compound **2** (234.0 mg, 0.58 mmol), prepared as described above, and iodomethane (124 mg, 0.87 mmol) in 3.0 mL of dimethylformamide was stirred

at room temperature (about 25°C) for about 12 h. The reaction mixture was then concentrated under reduced pressure to remove excess iodomethane. Triethylamine (1.74 mmol) in ethyl acetate (2.5 mL) was added to the mixture and the mixture was allowed to stir for about 2 h. The mixture was then concentrated under reduced pressure and purified using column chromatography (silica gel eluted with 2:1 hexane:ethyl acetate) to provide Compound **3** (65% yield). The identity of Compound **3** was confirmed using ^{1}H NMR.

Compound **3**: ^{1}H NMR ($CDCl_3$) δ 8.22 (dd, J = 1.6, 4.8 Hz, 1H), 7.63 (dd, J = 1.6, 7.8 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 6.90 (dd, J = 4.8, 7.8 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 5.14 (br, 1H), 4.64 (m,1 H), 4.07 (dd, J = 13.1 Hz, 1H), 3.75 (m, 1H), 3.50 (dt, J = 3.4, 13.1 Hz, 1H), 3.15 (dd, J = 3.4, 12.5 Hz, 1H), 3.02 (dt, J = 3.4, 12.5 Hz, 1H), 2.09 (s, 3H), 1.47 (d, J = 6.75 Hz, 3H), 1.33 (s, 9H) ppm.

A solution of Compound **3** (120 mg, 0.29 mmol), prepared as described above, and hydroxylamine (50 wt % in water, 383.0 mg, 5.8 mmol) in ethanol (1.5. mL) was stirred at about 80°C for about 2 h. The mixture was then cooled to room temperature (about 25°C), concentrated, and purified using column chromatography (silica gel eluted with gradient elution from 10:1 hexane:ethyl acetate to 2:1 hexane:ethyl acetate) to provide Compound **A1(c)**, *i.e.*, *N*-(4-tert-Butyl-phenyl)-4-(3-chloro-pyridin-2-yl)-*N*-hydroxy-(R)-2-methyl-piperazine-1-carboxamidine (71% yield). The identity of Compound **A1(c)** was confirmed using ^{1}H NMR.

Compound **A1(c)**: ^{1}H NMR ($CDCl_3$) δ 8.21 (dd, J = 1.6, 4.8 Hz, 1H), 7.61 (dd, J = 1.6, 7.8 Hz, 1H), 7.29 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 6.88 (dd, J = 4.8, 7.8 Hz, 1H), 6.68 (br, 1H), 3.67 (m,1 H), 3.50 (m, 1H), 3.35 (m, 2H), 3.10 (m, 2H), 1.63 (br, 1H), 1.32 (d, J = 6.75 Hz, 3H), 1.31 (s, 9H) ppm.

5.2 Example 2: Synthesis of Compound A1(d)

Compound **A1(d)** was prepared by a procedure that is analogous to that used to prepare Compound **A1(c)** except that (S)-2-methylpiperazine (Commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) was used in place of (R)-2-methylpiperazine. The identity of Compound **A1(d)**, *i.e.*, *N*-(4-tert-Butyl-phenyl)-4-(3-chloro-pyridin-2-yl)-*N*-hydroxy-(S)-2-methyl-piperazine-1-carboxamidine), was confirmed using ^{1}H NMR.

Compound **A1(d)**: ^{1}H NMR ($CDCl_3$) δ 8.21 (dd, J = 1.6, 4.8 Hz, 1H), 7.61 (dd, J = 1.6, 7.8 Hz, 1H), 7.29 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 6.88 (dd, J = 4.8, 7.8 Hz, 1H), 6.68 (br, 1H), 3.67 (m,1 H), 3.50 (m, 1H), 3.35 (m, 2H), 3.10 (m, 2H), 1.63 (br, 1H), 1.32 (d, J = 6.75 Hz, 3H), 1.31 (s, 9H) ppm.

5.3 Example 3: Synthesis of Compound A1(a)

Compound **A1(a)** was prepared by a procedure that is analagous to that used to prepare Compound **A1(c)** except that piperazine was used in place of (R)-2-methylpiperazine. The identity of Compound **A1(a)** was confirmed using ^{1}H NMR.

Compound **A1(a)**: ^{1}H NMR ($CDCl_3$) δ 8.21 (dd, J = 1.6, 4.8 Hz, 1H), 7.61 (dd, J = 1.6, 7.8 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 6.88 (dd, J = 4.8, 7.8 Hz, 1H), 6.68 (br, 1H), 3.35 (m, 4H), 3.25 (m, 4H), 1.63 (br, 1H), 1.28 (s, 9H) ppm.

5.4 Example 4: Synthesis of Compound A29(a)

Compound **A29(a)** was prepared by a procedure that is analogous to that used to prepare Compound **A1(a)** except that 2-chloro-3-methylpyridine was used in place of 2,3-dichloropyridine. The identity of Compound **A29(a)** was confirmed using ^{1}H NMR.

Compound **A29(a)**: ^{1}H NMR ($CDCl_3$) δ 8.18 (dd, J = 1.3, 4.8 Hz, 1H), 7.43 (dd, J = 1.3, 7.3 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 6.89 (dd, J = 4.8, 7.3 Hz, 1H), 6.73 (br, 1H), 3.23 (m, 4H), 3.16 (m, 4H), 2.28 (s, 3H), 1.63 (br, 1H), 1.31 (s, 9H) ppm.

5.5 Example 5: Synthesis of Compound A35(a)

Compound **A35(a)** was prepared by a procedure that is analogous to that used to prepare Compound **A29(a)** except that 4-(trifluoromethyl)-phenylisothiocyanate was used in place of 4-(*tert*-butyl)-phenylisothiocyanate. The identity of Compound **A35(a)**was confirmed using ^{1}H NMR.

Compound **A35(a)**: ^{1}H NMR ($CDCl_3$) δ 8.19 (dd, J = 1.2, 4.8 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.43 (dd, J = 1.2, 7.3 Hz, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.06 (br, 1H), 6.90 (dd, J = 4.9, 7.3 Hz, 1H), 6.72 (br, 1H), 3.25 (m, 4H), 3.18 (m, 4H), 2.19 (s, 3H) ppm.

5.6 Example 6: Synthesis of Compound A43(c)

Compound **A43(c)** was prepared by a procedure that is analogous to that used to prepare Compound **A1(c)** except that 2-chloro-3-trifluoromethylpyridine was used in place of 2,3-dichloropyridine. The identity of Compound **A43(c)** was confirmed using ^{1}H NMR.

Compound **A43(c)**: ^{1}H NMR ($CDCl_3$) δ 8.48 (dd, J = 1.5, 4.7 Hz, 1H), 7.91 (dd, J = 1.5, 7.8 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.07 (dd, J = 4.7, 7.8 Hz, 1H), 6.32 (br, 1H), 3.65 (m, 1H), 3.43 (m, 1H), 3.32 (m, 2H), 3.25 (m, 2H), 3.14 (m, 1H), 1.63 (br, 1H), 1.32 (s, 9H), 1.25 (d, J = 7.6 Hz, 3H) ppm.

5.7 Example 7: Synthesis of Compound A183(a)

Compound **A183(a)** was prepared by a procedure that is analogous to that used to prepare Compound **A1(a)** except that 2,3-dichloropyrazine was used in place of 2,3-dichloropyridine. The identity of Compound **A183(a)**was confirmed using ^{1}H NMR.

Compound **A183(a)**: ^{1}H NMR ($CDCl_3$) δ 8.21 (s, 1H), 7.89 (s, 1H), 729 (m, 2H), 7.18 (m, 2H), 6.68 (bs, 1H), 3.35 (bs, 4H), 3.25 (bs, 4H), 1.28 (s, 9H) ppm.

5.8 Example 8: Synthesis of Compound A267(a)

Compound **A267(a)** was prepared by a procedure that is analogous to that used to prepare Compound **A1(a)** except that 4,5-dichloro-2-thia-1,3-diazole was used in place of 2,3-dichloropyridine. The identity of Compound **A267(a)**was confirmed using ^{1}H NMR.

Compound **A267(a)**: ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 2H), 7.19 (m, 2H), 6.78 (bs, 1H), 3.55 (bs, 4H), 3.25 (bs, 4H), 1.28 (s, 9H) ppm).

5.9 Example 9: Synthesis of Compound A43(a)

Compound **A43(a)** was prepared by a procedure that is analogous to that used to prepare Compound **A1(a)** except that 2-chloro-3-trifluoromethylpyridine was used in place of 2,3-dichloropyridine. The identity of Compound **A43(a)**was confirmed using ^{1}H NMR.

Compound **A43(a)**: ^{1}H NMR ($CDCl_3$) δ 8.47-8.44 (m, 1H), 7.90-7.87 (m, 1H), 7.31-7.29 (m, 2H), 7.18-716 (m, 2H), 7.06-7.01 (m, 1H), 6.7- (s, 1H), 3.30-3.27 (m, 4H), 3.24-3.21 (m, 4H), 1.31 (s, 9H) ppm.

5.10 Example 10: Synthesis of Compound B1(a)

A solution of Compound **A1(a)** (77.4 mg, 0.20 mmol), prepared as described above in Example 5.3, in 1.5 mL of anhydrous dimethylformamide was added NaH (60 wt %, 8.4 mg, 0.21 mmol) and the resulting mixture was allowed to stir at room temperature (about 25°C) for about 0.5 h. Iodomethane (28.4 mg, 0.20 mmol) was then added to the reaction mixture and the mixture was allowed to stir at room temperature (about 25°C) for about 4 h. The reaction mixture was then quenched with water and extracted with diethyl ether. The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was then purified using column chromatography (silica gel eluted with gradient elution (10:1 hexane:ethyl acetate to 2:1 hexane:ethyl acetate) to provide Compound **B1(a)** (64% yield). The identity of Compound **B1(a)** was confirmed using ^{1}H NMR.

Compound **B1(a)**: ^{1}H NMR ($CDCl_3$) δ 8.21 (dd, J = 1.6, 4.8 Hz, 1H), 7.61 (dd, J = 1.6, 7.8 Hz, 1H), 7.29 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 6.88 (dd, J = 4.8, 7.8 Hz, 1H), 6.60 (br, 1H), 3.79 (s, 3H), 3.36 (m, 4H), 3.25 (m, 4H), 1.31 (s, 9H) ppm.

5.11 Example 11: Binding of Hydroxyiminopiperazine Compounds to mGluR5

The following assay can be used to demonstrate that Hydroxyiminopiperazine Compounds bind to mGluR5.

Cell cultures: Primary glial cultures are prepared from cortices of Sprague-Dawley 18 days old embryos. The cortices are dissected and then dissociated by trituration. The resulting cell homogenate is plated onto poly-D-lysine precoated T175 flasks (BIOCOAT, commercially available from Becton Dickinson and Company Inc. of Franklin Lakes, NJ) in Dulbelcco's Modified Eagle's Medium ("DMEM," pH 7.4), buffered with 25 mM HEPES, and supplemented with 15% fetal calf serum ("FCS," commercially available from Hyclone Laboratories Inc. of Omaha, NE), and incubated at 37°C and 5% CO_2. After 24 h, FCS supplementation is reduced to 10%. On day six, oligodendrocytes and microglia are removed by strongly tapping the sides of the flasks. One day following this purification step, secondary astrocytes cultures are established by subplating onto 96 poly-D-lysine precoated T175 flasks (BIOCOAT) at a density of 65,000 cells/well in DMEM and 10% FCS. After 24 h, the astrocytes are washed with serum free medium and then cultured in DMEM, without glutamate, supplemented with 0.5% FCS, 20 mM HEPES, 10 ng/mL epidermal growth factor ("EGF"), 1 mM sodium pyruvate, and 1X penicillin/streptomycin at pH 7.5 for 3 to 5 days at 37°C and 5% CO_2. The procedure allows the expression of the mGluR5 receptor by astrocytes, as demonstrated by S. Miller *et al.*, *J. Neuroscience* 15(9):6103-6109 (1995).

Assay Protocol: After 3-5 days incubation with EGF, the astrocytes are washed with 127 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 700 mM NaH_2PO_4, 2 mM $CaCl_2$, 5 mM $NaHCO_3$, 8 mM HEPES, 10 mM Glucose at pH 7.4 ("Assay Buffer") and loaded with the dye Fluo-4 (commercially available from Molecular Probes Inc. of Eugene, OR) using 0.1 mL of Assay Buffer containing Fluo-4 (3 mM final). After 90 minutes of dye loading, the cells are then washed twice with 0.2 mL Assay Buffer and resuspended in 0.1 mL of Assay Buffer. The plates containing the astrocytes are then transferred to a Fluorometric Imaging Plate reader (commercially available from Molecular Devices Corporation of Sunnyvale, CA) for the assessment of calcium mobilization flux in the presence of glutamate and in the presence or absence of antagonist. After monitoring fluorescence for 15 seconds to establish a base line, DMSO solutions containing various concentrations of

the Hydroxyiminopiperazine Compounds diluted in Assay Buffer (0.05 mL of 4X dilutions for competition curves) are added to the cell plate and fluorescence is monitored for 2 minutes. 0.05 mL of a 4X glutamate solution (agonist) is then added to each well to provide a final glutamate concentration in each well of 10 mM. Plate fluorescence is then monitored for an additional 60 seconds after agonist addition. The final DMSO concentration in the assay is 1.0%. In each experiment, fluorescence is monitored as a function of time and the data analyzed using Microsoft Excel and GraphPad Prism. Dose-response curves are fit using a non-linear regression to determine IC_{50} value. In each experiment, each data point is determined two times.

5.12 Example 12: *In Vivo* Assays for Prevention or Treatment of Pain

Test Animals: Each experiment uses rats weighing between 200-260 g at the start of the experiment. The rats are group-housed and have free access to food and water at all times, except prior to oral administration of a Hydroxyiminopiperazine Compound when food is removed for 16 h before dosing. A control group acts as a comparison to rats treated with a Hydroxyiminopiperazine Compound. The control group is administered the carrier for the Hydroxyiminopiperazine Compound. The volume of carrier administered to the control group is the same as the volume of carrier and Hydroxyiminopiperazine Compound administered to the test group.

Acute Pain: To assess the actions of the Hydroxyiminopiperazine Compounds for the treatment or prevention of acute pain the rat tail flick test can be used. Rats are placed inside a cotton pouch and the tail exposed to a focused beam of radiant heat at a point 3 cm from the tip using a tail flick unit (Model 7360, commercially available from Ugo Basile of Italy). Tail flick latencies are defined as the interval between the onset of the thermal stimulus and the flick of the tail. Animals not responding within 15 seconds are removed from the tail flick unit and assigned a withdrawal latency of 15 seconds. Tail flick latencies are measured immediately before (pre-treatment) and 1, 3, and 6 h following administration of a Hydroxyiminopiperazine Compound. Data are expressed as tail flick latency(s) and the percentage of the maximal possible effect (% MPE), *i.e.*, 15 seconds, is calculated as follows:

$$\%\ \text{MPE} = \frac{[\ (\text{post administration latency}) - (\text{pre-administration latency})\ ]}{(15\ \text{s pre-administration latency})} \times 100$$

The rat tail flick test is described in F.E. D'Amour *et al.*, "A Method for Determining Loss of Pain Sensation," *J. Pharmacol. Exp. Ther.* 72:74-79 (1941).

Acute pain can also be assessed by measuring the animal's response to noxious mechanical stimuli by determining the paw withdrawal threshold (PWT), as described below.

Inflammatory Pain: To assess the actions of the Hydroxyiminopiperazine Compounds for the treatment or prevention of inflammatory pain the Freund's complete adjuvant (FCA) model of inflammatory pain is used. FCA-induced inflammation of the rat hind paw is associated with the development of persistent inflammatory mechanical hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (L. Bartho *et al.*, "Involvement of Capsaicin-sensitive Neurones in Hyperalgesia and Enhanced Opioid Antinociception in Inflammation," *Naunyn-Schmiedeberg's Archives of Pharmacology* 342:666-670 (1990)). The left hind paw of each animal is administered a 50 μL intraplantar injection of 100% FCA. 24 h post injection, the animal is assessed for response to noxious mechanical stimuli by determining the PWT, as described below. Rats are then administered a single injection of 1, 3, 10, or 30 mg/Kg of either a Hydroxyiminopiperazine Compound, 30 mg/Kg indomethacin or carrier. Responses to noxious mechanical stimuli are then determined 2, 4, 6, and 24 h post administration. Percentage reversal of hyperalgesia for each animal is defined as:

$$\% \text{ Reversal} = \frac{[\text{(post administration PWT)} - \text{(pre-administration PWT)}]}{\text{(Baseline pre-administration PWT)}} \times 100$$

Neuropathic Pain: To assess the actions of the Hydroxyiminopiperazine Compounds for the treatment or prevention of neuropathic pain either the Seltzer model or the Chung model can be used.

In the Seltzer model, the partial sciatic nerve ligation model of neuropathic pain is used to produce neuropathic hyperalgesia in rats (Z. Seltzer *et al.*, "A Novel Behavioral Model of Neuropathic Pain Disorders Produced in Rats by Partial Sciatic Nerve Injury," *Pain* 43:205-218 (1990)). Partial ligation of the left sciatic nerve is performed under enflurane/O_2 inhalation anaesthesia. Following induction of anesthesia, the left thigh of the rat is shaved and the sciatic nerve exposed at high thigh level through a small incision

and is carefully cleared of surrounding connective tissues at a site near the trocanther just distal to the point at which the posterior biceps semitendinosus nerve branches off of the common sciatic nerve. A 7-0 silk suture is inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle and tightly ligated so that the dorsal 1/3 to 1/2 of the nerve thickness is held within the ligature. The wound is closed with a single muscle suture (7-0 silk) and a Michelle clip. Following surgery, the wound area is dusted with antibiotic powder. Sham-treated rats undergo an identical surgical procedure except that the sciatic nerve is not manipulated. Following surgery, animals are weighed and placed on a warm pad until they recover from anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animal is assessed for response to noxious mechanical stimuli by determining PWT, as described below, immediately prior to and 1, 3, and 6 h after drug administration for both the left rear paw and right rear paw of the animal. Percentage reversal of neuropathic hyperalgesia is defined as:

% reversal = 100 - [(right pre-administration PWT- left post-administration PWT) / (right pre-administration PWT-left pre-administration PWT)] x 100.

In the Chung model, the spinal nerve ligation model of neuropathic pain is used to produce mechanical hyperalgesia, themal hyperalgesia and tactile allodynia in rats. Surgery is performed under isoflurane/O_2 inhalation anaesthesia. Following induction of anaesthesia a 3 cm incision is made and the left paraspinal muscles are separated from the spinous process at the L_4 - S_2 levels. The L_6 transverse process is carefully removed with a pair of small rongeurs to identify visually the L_4 - L_6 spinal nerves. The left L_5 (or L_5 and L_6) spinal nerve(s) is isolated and tightly ligated with silk thread. A complete hemostasis is confirmed and the wound is sutured using non-absorbable sutures, such as nylon sutures or stainless steel staples. Sham-treated rats undergo an identical surgical procedure except that the spinal nerve(s) is not manipulated. Following surgery animals are weighed, administered a subcutaneous (s.c.) injection of saline or ringers lactate, the wound area is dusted with antibiotic powder and they are kept on a warm pad until they recover from the anesthesia. Animals are then be returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, immediately prior to and 1, 3, and 5 h after being administered a Hydroxyiminopiperazine Compound for both the left rear paw and right rear paw of the animal. The animal can also be assessed for response to noxious thermal stimuli or for

tactile allodynia, as described below. The Chung model for neuropathic pain is described in S.H. Kim, "An Experimental Model for Peripheral Neuropathy Produced by Segmental Spinal Nerve Ligation in the Rat," *Pain* 50(3):355-363 (1992).

Response to Mechanical Stimuli as an Assessment of Mechanical Hyperalgesia: The paw pressure assay can be used to assess mechanical hyperalgesia. For this assay, hind paw withdrawal thresholds (PWT) to a noxious mechanical stimulus are determined using an analgesymeter (Model 7200, commercially available from Ugo Basile of Italy) as described in C. Stein, "Unilateral Inflammation of the Hindpaw in Rats as a Model of Prolonged Noxious Stimulation: Alterations in Behavior and Nociceptive Thresholds," *Pharmacology Biochemistry and Behavior* 31:451-455 (1988). The maximum weight that can be applied to the hind paw is set at 250 g and the end point is taken as complete withdrawal of the paw. PWT is determined once for each rat at each time point and only the affected (ipsilateral) paw is tested.

Response to Thermal Stimuli as an Assessment of Thermal Hyperalgesia: The plantar test can be used to assess thermal hyperalgesia. For this test, hind paw withdrawal latencies to a noxious thermal stimulus are determined using a plantar test apparatus (commercially available from Ugo Basile of Italy) following the technique described by K. Hargreaves *et al.*, "A New and Sensitive Method for Measuring Thermal Nociception in Cutaneous Hyperalgesia," *Pain* 32(1):77-88 (1988). The maximum exposure time is set at 32 seconds to avoid tissue damage and any directed paw withdrawal from the heat source is taken as the end point. Three latencies are determined at each time point and averaged. Only the affected (ipsilateral) paw is tested.

Assessment of Tactile Allodynia: To assess tactile allodynia, rats are placed in clear, plexiglass compartments with a wire mesh floor and allowed to habituate for a period of at least 15 minutes. After habituation, a series of von Frey monofilaments are presented to the plantar surface of the left (operated) foot of each rat. The series of von Frey monofilaments consists of six monofilaments of increasing diameter, with the smallest diameter fiber presented first. Five trials are conducted with each filament with each trial separated by approximately 2 minutes. Each presentation lasts for a period of 4-8 seconds or until a nociceptive withdrawal behavior is observed. Flinching, paw withdrawal or licking of the paw are considered nociceptive behavioral responses.

5.13 Example 13: *In Vivo* Assays for Prevention or Treatment of Anxiety

The elevated plus maze test or the shock-probe burying test can be used to assess the anxiolytic activity of Hydroxyiminopiperazine Compounds in rats or mice.

The Elevated Plus Maze Test: The elevated plus maze consists of a platform with 4 arms, two open and two closed (50x10x50 cm enclosed with an open roof). Rats (or mice) are placed in the center of the platform, at the crossroad of the 4 arms, facing one of the closed arms. Time spent in the open arms vs the closed arms and number of open arm entries during the testing period are recorded. This test is conducted prior to drug administration and again after drug administration. Test results are expressed as the mean time spent in open arms and the mean number of entries into open arms. Known anxiolytic drugs increase both the time spent in open arms and number of open arm entries. The elevated plus maze test is described in D. Treit, "Animal Models for the Study of Anti-anxiety Agents: A Review," *Neuroscience & Biobehavioral Reviews* 9(2):203-222 (1985).

The Shock-Probe Burying Test: For the shock-probe burying test the testing apparatus consists of a plexiglass box measuring 40x30x40 cm, evenly covered with approximately 5 cm of bedding material (odor absorbent kitty litter) with a small hole in one end through which a shock probe (6.5 cm long and 0.5 cm in diameter) is inserted. The plexiglass shock probe is helically wrapped with two copper wires through which an electric current is administered. The current is set at 2 mA. Rats are habituated to the testing apparatus for 30 min on 4 consecutive days without the shock probe in the box. On test day, rats are placed in one corner of the test chamber following drug administration. The probe is not electrified until the rat touches it with its snout or fore paws, at which point the rat receives a brief 2 mA shock. The 15 min testing period begins once the rat receives its first shock and the probe remains electrified for the remainder of the testing period. The shock elicits burying behavior by the rat. Following the first shock, the duration of time the rat spends spraying bedding material toward or over the probe with its snout or fore paws (burying behavior) is measured as well as the number of contact-induced shocks the rat receives from the probe. Known anxiolytic drugs reduce the amount of burying behavior. In addition, an index of the rat's reactivity to each shock is scored on a 4 point scale. The total time spent immobile during the 15 min testing period is used as an index of general activity. The shock-probe burying test is described in D. Treit, 1985, *supra*.

5.14 Example 14: *In Vivo* Assays for Prevention or Treatment of an Addictive Disorder

The condition place preference test or drug self-administration test can be used to assess the ability of Hydroxyiminopiperazine Compounds to attenuate the rewarding properties of known drugs of abuse.

The Condition Place Preference Test: The apparatus for the conditioned place preference test consists of two large compartments (45x45x30 cm) made of wood with a plexiglass front wall. These two large compartments are distinctly different. Doors at the back of each large compartment lead to a smaller box (36x18x20 cm) box made of wood, painted grey, with a ceiling of wire mesh. The two large compartments differ in terms of shading (white vs black), level of illumination (the plexiglass door of the white compartment is covered with aluminum foil except for a window of 7x7 cm), texture (the white compartment has a 3 cm thick floor board (40x40 cm) with nine equally spaced 5 cm diameter holes and the black has a wire mesh floor), and olfactory cues (saline in the white compartment and 1 mL of 10% acetic acid in the black compartment). On habituation and testing days, the doors to the small box remain open, giving the rat free access to both large compartments.

The first session that a rat is placed in the apparatus is a habituation session and entrances to the smaller grey compartment remain open giving the rat free access to both large compartments. During habituation, rats generally show no preference for either compartment. Following habituation, rats are given 6 conditioning sessions. Rats are divided into 4 groups: carrier pre-treatment + carrier (control group), Hydroxyiminopiperazine Compound pre-treatment + carrier, carrier pre-treatment + morphine, Hydroxyiminopiperazine Compound pre-treatment + morphine. During each conditioning session the rat is injected with one of the drug combinations and confined to one compartment for 30 min. On the following day, the rat receives a carrier + carrier treatment and is confined to the other large compartment. Each rat receives three conditioning sessions consisting of 3 drug combination-compartment and 3 carrier-compartment pairings. The order of injections and the drug/compartment pairings are counterbalanced within groups. On the test day, rats are injected prior to testing (30 min to 1 h) with either morphine or carrier and the rat is placed in the apparatus, the doors to the grey compartment remain open and the rat is allowed to explore the entire apparatus for 20 min. The time spent in each compartment is recorded. Known drugs of abuse increase the time spent in the drug-paired compartment during the testing session. If the Hydroxyiminopiperazine Compound blocks the acquisition of morphine conditioned place preference (reward), there will be no difference in time spent in each side in rats pre-treated with a Hydroxyiminopiperazine Compound and the group will not be different from the group of rats that was given carrier + carrier in both compartments. Data will be analyzed as time spent in each compartment (drug combination-paired vs carrier-paired). Generally,

the experiment is repeated with a minimum of 3 doses of a Hydroxyiminopiperazine Compound.

The Drug Self-Administration Test: The apparatus for the drug self-administration test is a standard commercially available operant conditioning chamber. Before drug trials begin rats are trained to press a lever for a food reward. After stable lever pressing behavior is acquired, rats are tested for acquisition of lever pressing for drug reward. Rats are implanted with chronically indwelling jugular catheters for i.v. administration of compounds and are allowed to recover for 7 days before training begins. Experimental sessions are conducted daily for 5 days in 3 h sessions. Rats are trained to self-administer a known drug of abuse, such as morphine. Rats are then presented with two levers, an "active" lever and an "inactive" lever. Pressing of the active lever results in drug infusion on a fixed ratio 1 (FR1) schedule (*i.e.*, one lever press gives an infusion) followed by a 20 second time out period (signaled by illumination of a light above the levers). Pressing of the inactive lever results in infusion of excipient. Training continues until the total number of morphine infusions stabilizes to within ± 10% per session. Trained rats are then used to evaluate the effect of Hydroxyiminopiperazine Compounds pre-treatment on drug self-administration. On test day, rats are pre-treated with a Hydroxyiminopiperazine Compound or excipient and then are allowed to self-administer drug as usual. If the Hydroxyiminopiperazine Compound blocks the rewarding effects of morphine, rats pre-treated with the Hydroxyiminopiperazine Compound will show a lower rate of responding compared to their previous rate of responding and compared to excipient pre-treated rats. Data is analyzed as the change in number of drug infusions per testing session (number of infusions during test session – number of infusions during training session).

5.15 Example 15: Functional Assay for Characterizing mGluR 1 Antagonistic Properties

Functional assays for the characterization of mGluR 1 antagonistic properties are well known in the art. For example, the following procedure can be used.

A CHO-rat mGluR1 cell line is generated using cDNA encoding rat mGluR1 receptor (M. Masu and S. Nakanishi, *Nature* 349: 760-765 (1991)). The cDNA encoding rat mGluR1 receptor can be obtained from, *e.g.*, Prof. S. Nakanishi (Kyoto, Japan).

40,000 CHO-rat mGluR1 cells/well are plated into a Costar 3409, black, clear bottom, 96 well, tissue culture treated plate (commercially available from Fisher Scientific of Chicago, IL) and are incubated in Dulbecco's Modified Eagle's Medium (DMEM, pH 7.4) supplemented with glutamine, 10% FBS, 1% Pen/Strep, and 500 μg/mL

Geneticin for about 12 h. The CHO-rat mGluR1 cells are then washed and treated with Optimem medium (commercially available from Invitrogen, Carlsbad, CA) and incubated for a time period ranging from 1 to 4 hours prior to loading the cells with the dye Fluo-4 (commercially available from Molecular Probes Inc., Eugene OR). After incubation, the cell plates are washed with loading buffer (127 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 700 μM, NaH_2PO_4, 2 mM $CaCl_2$, 5 mM$NaHCO_3$, 8 mM HEPES, and 10 mM glucose, pH 7.4) and incubated with 3 μM Fluo-4 in 0.1 mL loading buffer for 90 min. The cells are then washed twice with 0.2 mL loading buffer, resuspended in 0.1 mL of loading buffer, and transferred to a Fluorometric Imaging Plate Reader (FLIPR) (commercially available from Molecular Devices Corp., Sunnyvale, CA) for measurement of calcium mobilization flux in the presence of glutamate and in the presence or absence of a Hydroxyiminopiperazine Compound.

To measure calcium mobilization flux, fluoresence is monitored for about 15 s to establish a baseline and DMSO solutions containing various concentrations of a Hydroxyiminopiperazine Compound ranging from about 50 μM to about 0.8 nM diluted in loading buffer (0.05 mL of a 4X dilution) are added to the cell plate and fluoresence is monitored for about 2 min. 0.05 mL of a 4X Glutamate solution (agonist) is then added to each well to provide a final glutamate concentration in each well of 10 μM and fluoresence is monitored for about 1 additional min. The final DMSO concentration in the assay is 1%. In each experiment fluoresence is monitored as a function of time and the data is analyzed using a non-linear regression to determine the IC_{50} value. In each expereiment each data point is determined twice.

5.16 Example 16: Binding of Hydroxyiminopiperazine Compounds to VR1

Methods for assaying compounds capable of inhibiting VR1 are well known to those skilled in the art, for example, those methods disclosed in U.S. Patent No. 6,239,267 to Duckworth *et al.*; U.S. Patent No. 6,406,908 to McIntyre *et al.*; or U.S. Patent No. 6,335,180 to Julius *et al.*

Binding of Compound **A1(a)** to VR1: Assay Protocol

Human VR1 cloning. Human spinal cord RNA (commercially available from Clontech, Palo Alto, CA) was used. Reverse transcription was conducted on 1.0 μg total RNA using Thermoscript Reverse Transcriptase (commercially available from Invitrogen, Carlsbad, CA) and oligo dT primers as detailed in its product description. Reverse transcription reactions were incubated at 55°C for 1 h, heat-inactivated at 85°C for 5 min, and RNase H-treated at 37°C for 20 min.

Human VR1 cDNA sequence was obtained by comparison of the human genomic sequence, prior to annotation, to the published rat sequence. Intron sequences were removed and flanking exonic sequences were joined to generate the hypothetical human cDNA. Primers flanking the coding region of human VR1 were designed as follows: forward primer, AAGATCTTCGCTGGTTGCACACTGGGCCACA; and reverse primer, GAAGATCTTCGGGGACAGTGACGGTTGGATGT.

PCR of VR1 was performed on one tenth of the Reverse transcription reaction mixture using Expand Long Template Polymerase and Expand Buffer 2 in a final volume of 50 μL according to the manufacturer's instructions (Roche Applied Sciences, Indianapolis, IN). After denaturation at 94°C for 2 min PCR amplification was performed for 25 cycles at 94°C for 15 sec, 58°C for 30 sec, and 68°C for 3 min followed by a final incubation at 72°C for 7 min to complete the amplification. A PCR product of ~2.8 kb was gel-isolated using a 1.0% agarose, Tris-Acetate gel containing 1.6 μg/mL of crystal violet and purified with a S.N.A.P. UV-Free Gel Purification Kit (commercially available from Invitrogen). The VR1 PCR product was cloned into the pIND/V5-His-TOPO vector (commercially available from Invitrogen) according to the manufacturer's instructions. DNA preparations, restriction enzyme digestions, and preliminary DNA sequencing were performed according to standard protocols. Full-length sequencing confirmed the identity of the human VR1.

Generation of inducible cell lines. Unless noted otherwise, cell culture reagents were purchased from Life Technologies of Rockville, MD. HEK293-EcR cells expressing the ecdysone receptor (commercially available from Invitrogen) were cultured in Growth Medium (Dulbecco's Modified Eagles Medium containing 10% fetal bovine serum (commercially available from HYCLONE, Logan, UT), lx penicillin/streptomycin, lx glutamine, 1 mM sodium pyruvate and 400 μg/mL Zeocin (commercially available from Invitrogen)). The VR1-pIND constructs were transfected into the HEK293-EcR cell line using Fugene transfection reagent (commercially available from Roche Applied Sciences, Basel, Switzerland). After 48 h, cells were transferred to Selection Medium (Growth Medium containing 300 μg/mL G418 (commercially available from Invitrogen)). Approximately 3 weeks later individual Zeocin/G418 resistant colonies were isolated and expanded. To identify functional clones, multiple colonies were plated into 96-well plates and expression was induced for 48 h using Selection Medium supplemented with 5 μM ponasterone A ("PonA") (commercially available from Invitrogen). On the day of assay, cells were loaded with Fluo-4 (a calcium-sensitive dye that is commercially available from

Molecular Probes, Eugene, OR) and CAP-mediated calcium influx was measured using a Fluorometric Imaging Plate Reader ("FLIPR") (commercially available from Molecular Devices Corp., Sunnyvale, CA) as described below. Functional clones were re-assayed, expanded, and cryopreserved.

pH-Based Assay. Two days prior to performing this assay, cells were seeded on poly-D-lysine-coated 96-well clear-bottom black plates (commercially available from Becton-Dickinson) at 75,000 cells/well in growth media containing 5 μM PonA (commercially available from Invitrogen) to induce expression. On the day of the assay, the plates were washed with 0.2 mL 1x Hank's Balanced Salt Solution (commercially available from Life Technologies) containing 1.6 mM $CaCl_2$ and 20 mM HEPES, pH 7.4 ("wash buffer"), and loaded using 0.1 mL of wash buffer containing Fluo-4 (3 μM final concentration, commercially available from Molecular Probes). After 1 h, the cells were washed twice with 0.2 mL wash buffer and resuspended in 0.05 mL 1x Hank's Balanced Salt Solution (commercially available from Life Technologies) containing 3.5 mM $CaCl_2$ and 10 mM Citrate, pH 7.4 ("assay buffer"). Plates were then transferred to a FLIPR (commercially available from Molecular Devices) for assay. Compound **A1(a)** was diluted in assay buffer, and 50 mL of the resultant solution were added to the cell plates and the solution monitored for two minutes. The final concentration of Compound **A1(a)** ranged from about 50 pM to about 3 μM. Agonist buffer (wash buffer titrated with 1N HCl to provide a solution having a pH of 5.5 when mixed 1:1 with assay buffer) (0.1 mL) was then added to each well, and the plates were incubated for 1 additional min. Data were collected over the entire time course and analyzed using Excel and Graph Pad Prism. Compound **A1(a)** when assayed according to this protocol had an IC_{50} of 40.9 ± 16.7 nM (n = 4).

Capsaicin-based Assay. Two days prior to performing this assay, cells were seeded in poly-D-lysine-coated 96-well clear-bottom black plates (50,000 cells/well) in growth media containing 5 μM PonA (commercially available from Invitrogen) to induce expression. On the day of the assay, the plates were washed with 0.2 mL 1x Hank's Balanced Salt Solution (commercially available from Life Technologies) containing 1 mM $CaCl_2$ and 20 mM HEPES, pH 7.4, and cells were loaded using 0.1 mL of wash buffer containing Fluo-4 (3 μM final). After one h, the cells were washed twice with 0.2 mL of wash buffer and resuspended in 0.1 mL of wash buffer. The plates were transferred to a FLIPR (commercially available from Molecular Devices) for assay. 50 μL of Compound **A1(a)** diluted with assay buffer were added to the cell plates and incubated for 2 min. The final concentration of Compound **A1(a)** ranged from about 50 pM to about 3 μM. Human

VR1 was activated by the addition of 50 μL of capsaicin (400 nM), and the plates were incubated for an additional 3 min. Data were collected over the entire time course and analyzed using Excel and GraphPad Prism. Compound **A1(a)** when assayed according to this protocol had an IC_{50} of 58.3 ± 10.1 nM (n = 4).

The results of the pH-based assay and the capsaicin-based assay demonstrate that Compound **A1(a)**, an illustrative Hydroxyiminopiperazine Compound, binds to and modulates the activity of human VR1 and, accordingly, is useful for treating ot preventing pain, UI, an ulcer, IBD, or IBS.

The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited, the entire disclosures of which are incorporated herein by reference.